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(57) Abstract

This invention provides for a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein. This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein. This invention also provides a method of inhibiting the proliferation of cancer cells. This invention also provides a method of treating cancer with a composition in an amount effective to result in an amount in apoptosis of the cells. This invention also provides a method of inhibiting the proliferation of virally infected cells. This invention also provides for a method of treating a virally-infected subject with a composition in an amount effective to result in apoptosis of the cells. This invention also provides for pharmaceutical compositions.

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This invention provides for a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein. This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein. This invention also provides a method of inhibiting the proliferation of cancer cells. This invention also provides a method of treating cancer with a composition in an amount effective to result in an amount in apoptosis of the cells. This invention also provides a method of inhibiting the proliferation of virally infected cells. This invention also provides for a method of treating a virally-infected subject with a composition in an amount effective to result in apoptosis of the cells. This invention also provides for pharmaceutical compositions.

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COMPOUNDS THAT INHIBIT INTERACTION BETWEEN SIGNAL-TRANSDUCING PROTEINS AND THE GLGF (PDZ/DHR) DOMAIN AND USES THEREOF

The invention disclosed herein was made with Government support under Grant No. R01GM55147-01 from the National Institutes of Health of the United States Department of Health and Human Services. Accordingly, the U.S. Government has certain rights in this invention.

BACKGROUND

Throughout this application, various publications are referenced by author and date. Full citations for these publications may be found listed alphabetically at the end of the specification immediately preceding Sequence Listing and the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

Fas (APO-1/CD95) and its ligand have been identified as important signal-mediators of apoptosis (Itoh, et al. 1991) The structural organization of Fas (APO-1/CD95) has suggested that it is a member of the tumor necrosis factor receptor superfamily, which also includes the p75 nerve growth factor receptor (NGFR) (Johnson, et al. 1986), the T-cell-activation marker CD27 (Camerini, et al. 1991), the Hodgkin-lymphoma-associated antigen CD30 (Smith, et al. (1993), the human B cell antigen CD40 (Stamenkovic, et al. 1989), and T cell antigen OX40 (Mallett, et al. 1990). Genetic mutations of both Fas and its ligand have been associated with lymphoproliferative and autoimmune disorders in mice (Watanabe-Fukunaga, et al. 1992; Takahashi, et al. 1994).

Furthermore, alterations of Fas expression level have been thought to lead to the induction of apoptosis in T-cells infected with human immunodeficiency virus (HIV) (Westendorp, et al. 1995).

Several Fas-interacting signal transducing molecules, such as Fas-associated phosphatase-1 (FAP-1)(Figure 1) (Sato, et al. 1995) FADD/MORT1/CAP-1/CAP-2 (Chinnaiyan, et al. 1995; Boldin, et al. 1995; Kischkel, et al. 1995) and RIP (Stanger, et al. 1995), have been identified using yeast two-hybrid and biochemical approaches. All but FAP-1 associate with the functional cell death domain of Fas and overexpression of FADD/MORT1 or RIP induces apoptosis in cells transfected with these proteins. In contrast, FAP-1 is the only protein that associates with the negative regulatory domain (C-terminal 15 amino acids) (Ito, et al. 1993) of Fas and that inhibits Fas-induced apoptosis.

FAP-1 (PTPN13) has several alternatively-spliced forms that are identical to PTP-BAS/hPTP1E/PTPL1, (Maekawa, et al. 1994; Banville, et al. 1994; Saras, et al. 1994) and contains a membrane-binding region similar to those found in the cytoskeleton-associated proteins, ezrin, (Gould et al. 1989) radixin (Funayama et al. 1991) moesin (Lankes, et al. 1991), neurofibromatosis type II gene product (NFII) (Rouleau, et al. 1993), and protein 4.1 (Conboy, et al. 1991), as well as in the PTPases PTPH1 (Yang, et al. 1991), PTP-MEG (Gu, et al. 1991), and PTPD1 (Vogel, et al. 1993). FAP-1 intriguingly contains six GLGF (PDZ/DHR) repeats that are thought to mediate intra-and inter-molecular interactions among protein domains. The third GLGF repeat of FAP-1 was first identified as a domain showing the specific interaction with the C-terminus of Fas receptor (Sato, et al. 1995). This suggests that the GLGF domain may play an important role in targeting proteins to the submembranous cytoskeleton

and/or in regulating biochemical activity. GLGF repeats have been previously found in guanylate kinases, as well as in the rat post-synaptic density protein (PSD-95) (Cho, et al. 1992), which is a homolog of the Drosophila tumor suppressor protein, lethal-(1)-disc-large-1 [*dlg-1*] (Woods, et al 1991; Kitamura, et al. 1994). These repeats may mediate homo- and hetero-dimerization, which could potentially influence PTPase activity, binding to Fas, and/or interactions of FAP-1 with other signal transduction proteins. Recently, it has also been reported that the different PDZ domains of proteins interact with the C-terminus of ion channels and other proteins (Figure 1) (TABLE 1) (Kornau, et al. 1995; Kim, et al. 1995; Matsumine, et al. 1996).

TABLE 1. Proteins that interact with PDZ domains.

Protein	C-terminal sequence	Associated protein	Reference
Fas (APO-1/CD95)	SLV	FAP-1	2
NMDA receptor NR2 subunit	SDV	PSD95	3
Shaker-type K+ channel	TDV	PSD95 & DLG	4
APC	TEV	DLG	5

SUMMARY OF THE INVENTION

This invention provides a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L) (Sequence I.D. No.: 1). Further, the cytoplasmic protein may contain the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L) (Sequence I.D. No.: 2), wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. In a preferred embodiment, the amino acid sequence is SLGI (Sequence I.D. No.: 3). Further, the invention provides for a composition when the signal-transducing protein has at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L)(Sequence I.D. No.: 4), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

This invention also provides for a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L). Further this invention provides for a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I) and a cytoplasmic protein.

This invention also provides for a method inhibiting the proliferation of cancer cells, specifically, where the cancer cells are derived from organs comprising the

colon, liver, breast, ovary, testis, lung, stomach, spleen, kidney, prostate, uterus, skin, head, thymus and neck, or the cells are derived from either T-cells or B-cells.

This invention also provides for a method of treating cancer in a subject in an amount of the composition of effective to result in apoptosis of the cells, specifically, where the cancer cells are derived from organs comprising the thymus, colon, liver, breast, ovary, testis, lung, stomach, spleen, kidney, prostate, uterus, skin, head and neck, or the cells are derived from either T-cells or B-cells.

This invention also provides for a method of inhibiting the proliferation of virally infected cells, specifically wherein the virally infected cells are infected with the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus, Adenovirus, Human T-cell lymphtropic virus, type 1 or HIV.

This invention also provides a pharmaceutical composition comprising compositions capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein.

This invention also provides a pharmaceutical composition comprising compounds identified to be capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Diagram of Fas-associated phosphatase-1 protein, showing the six GLGF (PDZ/DHR) domain repeats; comparison of similar membrane binding sites with other proteins and proteins that contain GLGF (PDZ/DHR) repeats.

Figures 2A, 2B, 2C and 2D. Mapping of the minimal region of the C-terminal of Fas required for the binding to FAP-1. Numbers at right show each independent clone (Figures 2C and 2D).

2A. Strategy for screening of a random peptide library by the yeast two-hybrid system.

2B. Alignment of the C-terminal 15 amino acids of Fas between human (Sequence I.D. No.: 5), rat (Sequence I.D. No.: 6), and mouse (Sequence I.D. No.: 7).

2C. The results of screening a semi-random peptide library. Top row indicates the amino acids which were fixed based on the homology between human and rat. Dash lines show unchanged amino acids.

2D. The results of screening a random peptide library (Sequence I.D. No.: 8, Sequence I.D. No.: 9, Sequence I.D. No.: 10, Sequence I.D. No.: 11, Sequence I.D. No.: 12, Sequence I.D. No.: 13, Sequence I.D. No.: 14, Sequence I.D. No.: 15, Sequence I.D. No.: 16, Sequence I.D. No.: 17, respectively).

Figures 3A, 3B and 3C. Inhibition assay of Fas/FAP-1 binding *in vitro*.

3A. Inhibition assay of Fas/FAP-1 binding using the C-terminal 15 amino acids of Fas. GST-Fas fusion protein (191-355) was used for *in vitro* binding assay (lane 1, 3-10). GST-Fas fusion protein (191-320) (lane 2) and 1 mM human PAMP (N-terminal 20 amino acids of proadrenomedullin, M.W. 2460.9)

(lane 3) were used as negative controls. The concentrations of the C-terminal 15 amino acids added were 1 (lane 4), 3 (lane 5), 10 (lane 6), 30 (lane 7), 100 (lane 8), 300 (lane 9), and 1000 μM (lane 10).

3B. Inhibition assay of Fas/FAP-1 binding using the truncated peptides corresponding to the C-terminal 15 amino acids of Fas. All synthetic peptides were acetylated for this inhibition assay (Sequence I.D. No.: 4, Sequence I.D. No.: 18, Sequence I.D. No.: 19, Sequence I.D. No.: 20, Sequence I.D. No.: 21, Sequence I.D. No.: 22, Sequence I.D. No.: 23, respectively).

3C. Inhibitory effect of Fas/FAP-1 binding using the scanned tripeptides.

Figures 4A, 4B, 4C and 4D.

4A. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in yeast.

4B. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in vitro.

4C. Immuno-precipitation of native Fas with GST-FAP-1.

4D. Inhibition of Fas/FAP-1 binding with Ac-SLV or Ac-SLY.

Figures 5A, 5B, 5C, 5D, 5E and 5F. Microinjection of Ac-SLV into the DLD-1 cell line. Triangles identify the cells both that were could be microinjected with Ac-SLV and that showed condensed chromatin identified. On the other hand, only one cell of the area appeared apoptotic when microinjected with Ac-SLY.

5A. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown in phase contrast.

5B. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown in phase contrast.

5C. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown stained with FITC.

5D. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown stained with FITC.

5E. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown with fluorescent DNA staining with Hoechst 33342.

5F. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown in fluorescent DNA staining with Hoechst 33342.

Figure 6. Quantitation of apoptosis in microinjected DLD-1 cells.

Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G, and 7H.

7A. Amino acid sequence of human nerve growth factor receptor (Sequence I.D. No.: 24).

7B. Amino acid sequence of human CD4 receptor (Sequence I.D. No. 25).

7C. The interaction of Fas-associated phosphatase-1 to the C-terminal of nerve growth factor receptor (NGFR)(p75).

7D. Amino acid sequence of human colorectal mutant cancer protein (Sequence I.D. No.: 26).

7E. Amino acid sequence of protein kinase C, alpha type.

7F. Amino acid sequence of serotonin 2A receptor (Sequence I,D. No.: 27).

7G. Amino acid sequence of serotonin 2B receptor (Sequence I.D. No.: 28).

7H. Amino acid sequence of adenomatosis polyposis coli protein (Sequence I.D. No.: 29).

Figure 8. Representation of the structural characteristics of p75 NGFR (low-affinity nerve growth factor receptor).

Figure 9. Comparison of the C-terminal ends of Fas and p75 NGFR.

Figure 10. In vitro interaction of ^{35}S-labeled FAP-1 with various receptors expressed as GST fusion proteins. The indicated GST fusion proteins immobilized on glutathione-Sepharose beads were incubated with in vitro translated, ^{35}S-labeled FAP-1 protein. After the beads were washed, retained FAP-1 protein was analyzed by SDS-PAGE and autoradiography.

Figures 11A and 11B. In vitro interaction ^{35}S-labeled FAP-1 with GST-p75 deletion mutants.

11A. Schematic representation of the GST fusion proteins containing the cytoplasmic domains of p75 and p75 deletion mutants. Binding of FAP-1 to the GST fusion proteins with various p75 deletion mutants is depicted at the right and is based on data from (11B).

11B. Interaction of in vitro translated, ^{35}S-labeled FAP-1 protein with various GST fusion proteins immobilized on glutathione-Sepharose beads. After the beads were washed, retained FAP-1 protein was analyzed by SDS-PAGE and autoradiography.

Figure 12. The association between LexA-C-terminal cytoplasmic region of p75NGFR and VP16-FAP-1. The indicated yeast strains were constructed by transformation and the growth of colonies was tested. +/- indicates the growth of colonies on his $^-$ plate.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, amino acid residues are abbreviated as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

In order to facilitate an understanding of the material which follows, certain frequently occurring methods and/or terms are best described in Sambrook, et al., 1989.

The present invention provides for a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids. Further, the cytoplasmic protein may contain the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L), wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. Specifically, in a preferred embodiment, the cytoplasmic protein contains the amino acid sequence SLGI.

The amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L) is also well-known in the art as "GLGF (PDZ/DHR) amino acid domain." As used herein, "GLGF (PDZ/DHR) amino acid domain" means the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L).

In a preferred embodiment, the signal-transducing protein

has at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

The compositions of the subject invention may be, but not limited to, antibodies, inorganic compounds, organic compounds, peptides, peptidomimetic compounds, polypeptides or proteins, fragments or derivatives which share some or all properties, e.g. fusion proteins. The composition may be naturally occurring and obtained by purification, or may be non-naturally occurring and obtained by synthesis.

Specifically, the composition may be a peptide containing the sequence (S/T)-X-(V/I/L)-COOH, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids. In preferred embodiments, the peptide contains one of the following sequences: DSENSNFRNEIQSLV, RNEIQSLV, NEIQSLV, EIQSLV, IQSLV, QSLV, SLV, IPPDSEDGNEEQSLV, DSEMYNFRSQLASVV, IDLASEFLFLSNSFL, PPTCSQANSGRISTL, SDSNMNMNELSEV, QNFRTYIVSFV, RETIESTV, RGFISSLV, TIQSVI, ESLV. A further preferred embodiment would be an organic compound which has the sequence Ac-SLV-COOH, wherein the Ac represents an acetyl and each - represents a peptide bond.

An example of the subject invention is provided <u>infra</u>. Acetylated peptides may be automatically synthesized on

an Advanced ChemTech ACT357 using previously published procedures by analogy. Wang resin was used for each run and N^{α}-Fmoc protection was used for all amino acids, and then 20% piperidine/DMF and coupling was completed using DIC/HOBt and subsequently HBTU/DIEA. After the last amino acid was coupled, the growing peptide on the resin was acetylated with Ac_2O/DMF. The acetylated peptide was purified by HPLC and characterized by FAB-MS and ^{1}H-NMR.

Further, one skilled in the art would know how to construct derivatives of the above-described synthetic peptides coupled to non-acetyl groups, such as amines.

This invention also provides for a composition capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein.

The compositions of the subject invention includes antibodies, inorganic compounds, organic compounds, peptides, peptidomimetic compounds, polypeptides or proteins, fragments or derivatives which share some or all properties, e.g. fusion proteins.

This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses

separating the alternative amino acids, which comprises (a) contacting the cytoplasmic protein bound to the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the signal-transducing protein bound to the cytoplasmic protein and the bound cytoplasmic protein to form a complex; and (b) detecting the displaced signal-transducing protein or the complex formed in step (a) wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein.

The inhibition of the specific binding between the signal-transducing protein and the cytoplasmic protein may affect the transcription activity of a reporter gene.

Further, in step (b), the displaced cytoplasmic protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the signal-transducing protein is displaced.

As used herein, the "transcription activity of a reporter gene" means that the expression level of the reporter gene will be altered from the level observed when the signal-transducing protein and the cytoplasmic protein are bound. One can also identify the compound by detecting other biological functions dependent on the binding between the signal-transducing protein and the cytoplasmic protein. Examples of reporter genes are numerous and well-known in the art, including, but not limited to, histidine resistant genes, ampicillin resistant genes, β-galactosidase gene.

Further the cytoplasmic protein may be bound to a solid support. Also the compound may be bound to a solid support and comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

An example of the method is provided infra. One can identify a compound capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein using direct methods of detection such as immuno-precipitation of the cytoplasmic protein and the compound bound to a detectable marker. Further, one could use indirect methods of detection that would detect the increase or decrease in levels of gene expression. As discussed infra, one could construct synthetic peptides fused to a LexA DNA binding domain. These constructs would be transformed into the L40-strain with an appropriate cell line having an appropriate reporter gene. One could then detect whether inhibition had occurred by detecting the levels of expression of the reporter gene. In order to detect the expression levels of the reporter gene, one skilled in the art could employ a variety of well-known methods, e.g. two-hybrid systems in yeast, mammals or other cells.

Further, the contacting of step (a) may be in vitro, in vivo, and specifically in an appropriate cell, e.g. yeast cell or mammalian cell. Examples of mammalian cells include, but not limited to, the mouse fibroblast cell NIH 3T3, CHO cells, HeLa cells, Ltk$^-$ cells, Cos cells, etc.

Other suitable cells include, but are not limited to, prokaryotic or eukaryotic cells, e.g. bacterial cells (including gram positive cells), fungal cells, insect cells, and other animals cells.

Further, the signal-transducing protein may be a cell surface receptor, signal transducer protein, or a tumor suppressor protein. Specifically, the cell surface protein is the Fas receptor and may be expressed in cells derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, lung, stomach, prostate, uterus, skin, head, and neck, or expressed in cells comprising T-cells and B-cells. In a preferred embodiment, the T-cells are Jurkat T-cells.

Further, the cell-surface receptor may be a CD4 receptor, p75 receptor, serotonin 2A receptor, or serotonin 2B receptor.

Further, the signal transducer protein may be Protein Kinase-C-α-type.

Further, the tumor suppressor protein may be a adenomatosis polyposis coli tumor suppressor protein or colorectal mutant cancer protein.

Further, the cytoplasmic protein contains the amino acid sequence SLGI, specifically Fas-associated phosphatase-1.

This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein which comprises (a) contacting the signal-transducing protein bound to the cytoplasmic protein with

a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the cytoplasmic protein bound to the signal-transducing protein and bound signal-transducing protein to form a complex; and (b) detecting the displaced cytoplasmic protein or the complex of step (a), wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein. The inhibition of the specific binding between the signal-transducing protein and the cytoplasmic protein affects the transcription activity of a reporter gene. Further, in step (b), the displaced signal-transducing protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the cytoplasmic protein is displaced.

Further, in step (b), the displaced cytoplasmic protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the signal-transducing protein is displaced.

As used herein, the "transcription activity of a reporter gene" means that the expression level of the reporter gene will be altered from the level observed when the signal-transducing protein and the cytoplasmic protein are bound. One can also identify the compound by detecting other biological functions dependent on the binding between the signal-transducing protein and the

cytoplasmic protein. Examples of reporter genes are numerous and well-known in the art, including, but not limited to, histidine resistant genes, ampicillin resistant genes, β-galactosidase gene.

Further, the cytoplasmic protein may be bound to a solid support or the compound may be bound to a solid support, comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

An example of the method is provided infra. One could identify a compound capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein using direct methods of detection such as immuno-precipitation of the cytoplasmic protein and the compound bound with a detectable marker. Further, one could use indirect methods of detection that would detect the increase or decrease in levels of gene expression. As discussed infra, one could construct synthetic peptides fused to a LexA DNA binding domain. These constructs would be transformed into L40-strain with an appropriate cell line having a reporter gene. One could then detect whether inhibition had occurred by detecting the levels of the reporter gene. Different methods are also well known in the art, such as employing a yeast two-hybrid system to detect the expression of a reporter gene.

Further the contacting of step (a) can be in vitro or in vivo, specifically in a yeast cell or a mammalian cell. Examples of mammalian cells include, but not limited to, the mouse fibroblast cell NIH 3T3, CHO cells, HeLa cells, Ltk^- cells, Cos cells, etc.

Other suitable cells include, but are not limited to, prokaryotic or eukaryotic cells, e.g. bacterial cells

(including gram positive cells), fungal cells, insect cells, and other animals cells.

Further, the signal-transducing protein is a cell surface receptor, signal transducer protein, or a tumor suppressor protein. Specifically, the cell surface protein is the Fas receptor and is expressed in cells derived from organs comprising thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or expressed in cells comprising T-cells and B-cells. In a preferred embodiment, the T-cells are Jurkat T-cells.

Further, the cell-surface receptor may be a CD4 receptor, p75 receptor, serotonin 2A receptor, or serotonin 2B receptor.

Further, the signal transducer protein may be Protein Kinase-C-α-type.

Further, the tumor suppressor protein may be a adenomatosis polyposis coli tumor suppressor protein or colorectal mutant cancer protein.

Further, the cytoplasmic protein contains the amino acid sequence SLGI, specifically Fas-associated phosphatase-1.

This invention also provides a method of inhibiting the proliferation of cancer cells comprising the above-described composition, specifically, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

This invention also provides a method of inhibiting the proliferation of cancer cells comprising the compound identified by the above-described method, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

The invention also provides a method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the above-described composition effective to result in apoptosis of the cells, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

As used herein "apoptosis" means programmed cell death of the cell. The mechanisms and effects of programmed cell death differs from cell lysis. Some observable effects of apoptosis are: DNA fragmentation and disintegration into small membrane-bound fragments called apoptotic bodies.

Means of detecting whether the composition has been effective to result in apoptosis of the cells are well-known in the art. One means is by assessing the morphological change of chromatin using either phase contrast or fluorescence microscopy.

The invention also provides for a method of inhibiting the proliferation of virally infected cells comprising the above-described composition or the compound identified by the above-described, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr

virus, influenza virus, Papilloma virus, Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

The invention also provides a method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells the above-described composition effective to result in apoptosis of the cells or the compound identified by the above-described method of claim 27 effective to result in apoptosis of the cells, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus, Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

Means of detecting whether the composition has been effective to result in apoptosis of the cells are well-known in the art. One means is by assessing the morphological change of chromatin using either phase contrast or fluorescence microscopy.

This invention also provides for a pharmaceutical composition comprising the above-described composition of in an effective amount and a pharmaceutically acceptable carrier.

This invention also provides for a pharmaceutical composition comprising the compound identified by the above-described method of in an effective amount and a pharmaceutically acceptable carrier.

This invention further provides a composition capable of specifically binding a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X

represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids. The composition may contain the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids. In a preferred embodiment, the composition contains the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L). wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. In another preferred embodiment, the composition contains the amino acid sequence SLGI.

This invention further provides a method for identifying compounds capable of binding to a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, which comprises (a) contacting the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to bind to the signal-transducing protein to form a complex; and (b) detecting the complex formed in step (a) so as to identify a compound capable of binding to the signal-transducing protein. Specifically, the identified compound contains the amino acid sequence (G/S/A/E)-L-G-(F/I/L). In a further preferred embodiment, the identified compound contains the amino acid sequence SLGI.

Further, in the above-described method, the signal-

transducing protein may be bound to a solid support. Also, the compound may be bound to a solid support, and may comprise an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

Further, the signal-transducing protein may be a cell-surface receptor or a signal transducer. Specifically, the signal-transducing protein may be the Fas receptor, CD4 receptor, p75 receptor, serotonin 2A receptor, serotonin 2B receptor, or protein kinase-C-α-type.

This invention also provides a method of restoring negative regulation of apoptosis in a cell comprising the above-described composition or a compound identified by the above-described method.

As used herein "restoring negative regulation of apoptosis" means enabling the cell from proceeding onto programmed cell death.

For example, cells that have functional Fas receptors and Fas-associated phosphatase 1 do not proceed onto programmed cell death or apoptosis due to the negative regulation of Fas by the phosphatase. However, if Fas-associated phosphatase 1 is unable to bind to the carboxyl terminus of the Fas receptor ((S/T)-X-(V/L/I) region) , e.g. mutation or deletion of at least one of the amino acids in the amino acid sequence (G/S/A/E)-L-G-(F/I/L), the cell will proceed to apoptosis. By introducing a compound capable of binding to the carboxyl terminus of the Fas receptor, one could mimic the effects of a functional phosphatase and thus restore the negative regulation of apoptosis.

This invention also provides a method of preventing apoptosis in a cell comprising the above-described

composition or a compound identified by the above-described method.

This invention also provides a means of treating pathogenic conditions caused by apoptosis of relevant cells comprising the above-described composition or the compound identified by the above-described method.

This invention is illustrated in the Experimental Details section which follows. These sections are set forth to aid in an understanding of the invention but are not intended to, and should not be construed to, limit in any way the invention as set forth in the claims which follow thereafter.

FIRST SERIES OF EXPERIMENTS

Experimental Details

Methods and Materials

1. Screening a semi-random and random peptide library.

To create numerous mutations in a restricted DNA sequence, PCR mutagenesis with degenerate oligonucleotides was employed according to a protocol described elsewhere (Hill, et al. 1987). Based on the homology between human and rat, two palindromic sequences were designed for construction of semi-random library. The two primers used were 5'-CGGAATTCNNNNNNNNNAACAGCNNNNNNNNNAATGAANNNCAAAGTCTGNNNTGAGGATCCTCA-3' (Seq. I.D. No.: 30) and 5'-CGGAATTCGACTCAGAANNNNNNAACTTCAGANNNNNNATCNNNNNNNNNGTCTGAGGATCCTCA-3' (Seq. I.D. No.: 31). Briefly, the two primers (each 200 pmol), purified by HPLC, were annealed at 70 °C for 5 minutes and cooled at 23 °C for 60 minutes. A Klenow fragment (5 U) was used for filling in with a dNTP mix (final concentration, 1 mM per each dNTP) at 23°C for 60 minutes. The reaction was stopped with 1 μl of 0.5 M EDTA and the DNA was purified with ethanol precipitation. The resulting double-stranded DNA was digested with EcoRI and BamHI and re-purified by electrophoresis on non-denaturing polyacrylamide gels. The double-strand oligonucleotides were then ligated into the EcoRI-BamHI sites of the pBTM116 plasmid. The ligation mixtures were electroporated into the *E. coli* XL1-Blue MRF' (Stratagene) for the plasmid library. The large scale transformation was carried out as previously reported. The plasmid library was transformed into L40-strain cells (*MATa, trp1, leu2, his3, ade2, LYS2:(lexAop)^4-HIS3, URA3::(lexAop)^8-lacZ*) carrying the plasmid pVP16-31 containing a FAP-1 cDNA (Sato, et al.

1995). Clones that formed on histidine-deficient medium (His^+) were transferred to plates containing 40 μg/ml X-gal to test for a blue reaction product (ß-gal^+) in plate and filter assays. The clones selected by His^+ and ß-gal^+ assay were tested for further analysis. The palindromic oligonucleotide, 5'-CGGAATTC-$(NNN)_{4-15}$-TGAGGATCCTCA-3' (Seq. I.D. No. 32), was used for the construction of the random peptide library.

2. Synthesis of peptides

Peptides were automatically synthesized on an Advanced ChemTech ACT357 by analogy to published procedures (Schnorrenberg and Gerhardt, 1989). Wang resin (0.2-0.3 mmole scale) was used for each run and N^α-Fmoc protection was employed for all amino acids. Deprotection was achieved by treatment with 20% piperidine/DMF and coupling was completed using DIC/HOBt and subsequent HBTU/DIEA. After the last amino acid was coupled, the growing peptide on the resin was acetylated with Ac_2O/DMF. The peptide was cleaved from the resin with concomitant removal of all protecting groups by treating with TFA. The acetylated peptide was purified by HPLC and characterized by FAB-MS and ^{1}H-NMR.

3. Inhibition asssay of Fas/FAP-1 binding using the C-terminal 15 amino acids of Fas.

HFAP-10 cDNA (Sato, et al. 1995) subcloned into the Bluescript vector pSK-II (Stratagene) was in vitro-translated from an internal methionine codon in the presence of ^{35}S-L-methionine using a coupled in vitro transcription/translation system (Promega, TNT lysate) and T7 RNA polymerase. The resulting ^{35}S-labeled protein was incubated with GST-Fas fusion proteins that had been immobilized on GST-Sepharose 4B affinity beads

(Pharmacia) in a buffer containing 150 mM NaCl, 50 mM Tris [pH 8.0], 5 mM DTT, 2 mM EDTA, 0.1 % NP-40, 1 mM PMSF, 50 μg/ml leupeptin, 1 mM Benzamidine, and 7 μg/ml pepstatin for 16 hours at 4 °C. After washing vigorously 4 times in the same buffer, associated proteins were recovered with the glutathione-Sepharose beads by centrifugation, eluted into boiling Laemmli buffer, and analyzed by SDS-PAGE and fluorography.

4. Inhibition assay of terminal 15 amino acids of Fas and inhibitory effect of Fas/FAP-1 binding using diverse tripeptides.

In vitro-translated [^{35}S]HFAP-1 was purified with a NAP-5 column (Pharmacia) and incubated with 3 μM of GST-fusion proteins for 16 hours at 4°C. After washing 4 times in the binding buffer, radioactivity incorporation was determined in a b counter. The percentage of binding inhibition was calculated as follows: percent inhibition = [radioactivity incorporation using GST-Fas (191-335) with peptides - radioactivity incorporation using GST-Fas (191-320) with peptides] / [radioactivity incorporation using GST-Fas (191-335) without peptides - radioactivity incorporation using GST-Fas (191-320) without peptides]. n=3.

5. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in yeast and in vitro.

The bait plasmids, pBTM116 (LexA)-SLV, -PLV, -SLY, and -SLA, were constructed and transformed into L40-strain with pVP16-FAP-1 or -ras. Six independent clones from each transformants were picked up for the analysis of growth on histidine-deficient medium. GST-Fas, -SLV, and PLV were purified with GST-Sepharose 4B affinity beads (Pharmacia). The methods for in vitro binding are described above.

6. Immuno-precipitation of native Fas with GST-FAP-1 and inhibition of Fas/FAP-1 binding with Ac-SLV.

GST-fusion proteins with or without FAP-1 were incubated with cell extracts from Jurkat T-cells expressing Fas. The bound Fas was detected by Western analysis using anti-Fas monoclonal antibody (F22120, Transduction Laboratories). The tripeptides, Ac-SLV and Ac-SLY were used for the inhibition assay of Fas/FAP-1 binding.

7. Microinjection of Ac-SLV into the DLD-1 cell line. DLD-1 human colon cancer cells were cultured in RPMI 1640 medium containing 10% FCS. For microinjection, cells were plated on CELLocate (Eppendorf) at 1 X 10^5 cells/2 ml in a 35 mm plastic culture dish and grown for 1 day. Just before microinjection, Fas monoclonal antibodies CH11 (MBL International) was added at the concentration of 500 ng/ml. All microinjection experiments were performed using an automatic microinjection system (Eppendorf transjector 5246, micro-manipulator 5171 and Femtotips) (Pantel, et al. 1995). Synthetic tripeptides were suspended in 0.1% (w/v) FITC-Dextran (Sigma)/K-PBS at the concentration of 100 mM. The samples were microinjected into the cytoplasmic region of DLD-1 cells. Sixteen to 20 hours postinjection, the cells were washed with PBS and stained with 10 μg/ml Hoechst 33342 in PBS. After incubation at 37°C for 30 minutes, the cells were photographed and the cells showing condensed chromatin were counted as apoptotic.

8. Quantitation of apoptosis in microinjected DLD-1 cells.

For each experiment, 25-100 cells were microinjected. Apoptosis of microinjected cells was determined by assessing morphological changes of chromatin using phase contrast and fluorescence microscopy (Wang, et al., 1995;

McGahon, et al., 1995). The data are means +/- S.D. for two or three independent determinations.

Discussion

In order to identify the minimal peptide stretch in the C-terminal region of the Fas receptor necessary for FAP-1 binding, an *in vitro* inhibition assay of Fas/FAP-1 binding was used using a series of synthetic peptides as well as yeast two-hybrid system peptide libraries (Figure 2A). First, semi-random libraries (based on the homology between human and rat Fas) (Figures 2B and 2C) of 15 amino acids fused to a LexA DNA binding domain were constructed and co-transformed into yeast strain L40 with pVP16-31 (Sato, et al. 1995) that was originally isolated as FAP-1. After the selection of 200 His^+ colonies from an initial screen of 5.0 X 10^6 (Johnson, et al. 1986) transformants, 100 colonies that were β-galactosidase positive were picked for further analysis. Sequence analysis of the library plasmids encoding the C-terminal 15 amino acids revealed that all of the C-termini were either valine, leucine or isoleucine residues. Second, a random library of 4-15 amino acids fused to a LexA DNA binding domain was constructed and screened according to this strategy (Figure 2D). Surprisingly, all of the third amino acid residues from the C-termini were serine, and the results of C-terminal amino acid analyses were identical to the screening of the semi-random cDNA libraries. No other significant amino acid sequences were found in these library screenings, suggesting that the motifs of the last three amino acids (tS-X-V/L/I) are very important for the association with the third PDZ domain of FAP-1 and play a crucial role in protein-protein interaction as well as for the regulation of Fas-induced apoptosis. To further confirm whether the last three amino acids are necessary and sufficient for Fas/FAP-1 binding, plasmids of the LexA-SLV, -PLV, -PLY,

-SLY, and -SLA fusion proteins were constructed and co-transformed into yeast with pVP16-FAP-1. The results showed that only LexA-SLV associated with FAP-1, whereas LexA-PLV, -PLY, -SLY, and -SLA did not (Figure 4A). In vitro binding studies using various GST-tripeptide fusions and *in vitro*-translated FAP-1 were consistent with these results (Figure 4B).

In addition to yeast two-hybrid approaches, *in vitro* inhibition assay of Fas/FAP-1 binding was also used. First, a synthetic peptide of the C-terminal 15 amino acids was tested whether it could inhibit the binding of Fas and FAP-1 *in vitro* (Figure 3A). The binding of *in vitro*-translated FAP-1 to GST-Fas was dramatically reduced and dependent on the concentration of the synthetic 15 amino acids of Fas. In contrast with these results, human PAMP peptide (Kitamura, et al. 1994) as a negative control had no effect on Fas/FAP-1 binding activity under the same biochemical conditions. Second, the effect of truncated C-terminal synthetic peptides of Fas on Fas/FAP-1 binding *in vitro* was examined. As shown in Figure 3B, only the three C-terminal amino acids (Ac-SLV) were sufficient to obtain the same level of inhibitory effect on the binding of FAP-1 to Fas as achieved with the 4-15 synthetic peptides. Furthermore, Fas/FAP-1 binding was extensively investigated using the scanned tripeptides to determine the critical amino acids residues required for inhibition (Figure 3C). The results revealed that the third amino acids residues from the C-terminus, and the C-terminal amino acids having the strongest inhibitory effect were either serine or threonine; and either valine, leucine, or isoleucine, respectively. However, there were no differences among the second amino acid residues from the C-terminus with respect to their inhibitory effect on Fas/FAP-1 binding. These results were consistent with those of the yeast two-hybrid system (Figures 2C and 2D). Therefore, it was

concluded that the C-terminal three amino acids (SLV) are critical determinants of Fas binding to the third PDZ domain of FAP-1 protein.

To further substantiate that the PDZ domain interacts with *t*S/T-X-V/L/I under more native conditions, GST-fused FAP-1 proteins were tested for their ability to interact with Fas expressed in Jurkat T-cells. The results revealed that the tripeptide Ac-SLV, but not Ac-SLY, abolished in a dose-dependent manner the binding activity of FAP-1 to Fas proteins extracted from Jurkat T-cells (Figures 4C and 4D). This suggests that the C-terminal amino acids *t*SLV are the minimum binding site for FAP-1, and that the amino acids serine and valine are critical for this physical association.

To next examine the hypothesis that the physiological association between the C-terminal three amino acids of Fas and the third PDZ domain of FAP-1 is necessary for the *in vivo* function of FAP-1 as a negative regulator of Fas-mediated signal transduction, a microinjection experiment was employed with synthetic tripeptides in a colon cancer cell line, DLD-1, which expresses both Fas and FAP-1, and is resistant to Fas-induced apoptosis. The experiments involved the direct microinjection of the synthetic tripeptides into the cytoplasmic regions of single cells and the monitoring of the physiological response to Fas-induced apoptosis *in vivo*. The results showed that microinjection of Ac-SLV into DLD-1 cells dramatically induced apoptosis in the presence of Fas-monoclonal antibodies (CH11, 500 ng/ml) (Figures 5A, 5E and Figure 6), but that microinjection of Ac-SLY and PBS/K did not (Figures 5B, 5F and Figure 6). These results strongly support the hypothesis that the physical association of FAP-1 with the C-terminus of Fas is essential for protecting cells from Fas-induced apoptosis.

In summary, it was found that the C-terminal SLV of Fas is alone necessary and sufficient for binding to the third PDZ domain of FAP-1. Secondly, it is proposed that the new consensus motif of tS/T-X-V/L/I for such binding to the PDZ domain, instead of tS/T-X-V. It is therefore possible that FAP-1 plays important roles for the modulation of signal transduction pathways in addition to its physical interaction with Fas. Thirdly, it is demonstrated that the targeted induction of Fas-mediated apoptosis in colon cancer cells by direct microinjection of the tripeptide Ac-SLV. Further investigations including the identification of a substrate(s) of FAP-1 and structure-function analysis will provide insight to the potential therapeutic applications of Fas/FAP-1 interaction in cancer as well as provide a better understanding of the inhibitory effect of FAP-1 on Fas-mediated signal transduction.

SECOND SERIES OF EXPERIMENTS

FAP-1 was originally identified as a membrane-associated protein tyrosine phosphatase which binds to the C-terminus of Fas, and possesses six PDZ domains (also known as DHR domain or GLGF repeat). PDZ domain has recently been shown as a novel module for specific protein-protein interaction, and it appears to be important in the assembly of membrane proteins and also in linking signaling molecules in a multiprotein complex. In recent comprehensive studies, it was found that the third PDZ domain of FAP-1 specifically recognized the sequence motif t(S/T)-X-V and interacts with the C-terminal three amino acids SLV of Fas (Fig. 9). In order to investigate the possibility that FAP-1 also interacts with the C-terminal region of p75NGFR (Fig. 8), an in vitro binding assay, was performed as well as, a yeast two-hybrid analysis by using a series of deletion mutants of p75NGFR. The results revealed that the C-terminal cytoplasmic region of p75NGFR, which is highly conserved among all species, interacts with FAP-1 (Fig. 10). Furthermore, the C-terminal three amino acids SPV of p75NGFR were necessary and sufficient for the interaction with the third PDZ domain of FAP-1 (Fig. 11A and 11B). Since FAP-1 expression was found highest in fetal brain, these findings imply that interaction of FAP-1 with p75NGFR plays an important role for signal transduction pathway via p75NGFR in neuronal cells as well as in the formation of the initial signal-transducing complex for p75NGFR.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Takaaki Sato and Junn Yanagisawa

(ii) TITLE OF INVENTION: COMPOUNDS THAT INHIBIT THE INTERACTION BETWEEN SIGNAL-TRANSDUCING PROTEINS AND THE GLGF (PDZ/DHR) DOMAIN AND USES THEREOF

(iii) NUMBER OF SEQUENCES: 33

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(C) CITY: New York
(D) STATE: New York
(E) COUNTRY: U.S.A.
(F) ZIP: 10036

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: Not Yet Known
(B) FILING DATE: 18-JUL-1997
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: White, John P
(B) REGISTRATION NUMBER: 28,678
(C) REFERENCE/DOCKET NUMBER: 0575/48962-A-PCT/JPW/JKM

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (212) 278-0400
(B) TELEFAX: (212) 391-0525

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Gly/Ser/Ala/Glu Leu Gly Phe/Ile/Leu
1

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys/Arg/Gln Xaa(n) Gly/Ser/Ala/Glu Leu Gly Phe/Ile/Leu
1 5

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ser Leu Gly Ile
1

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Ser/Thr Xaa Val/Ile/Leu
1

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ser Ile Ser Asn Ser Arg Asn Glu Asn Glu Gly Gln Ser Leu Glu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ser Thr Pro Asp Thr Gly Asn Glu Asn Glu Gly Gln Cys Leu Glu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Glu Ser Leu Val
1

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Thr Ile Gln Ser Val Ile
1 5

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Arg Gly Phe Ile Ser Ser Leu Val
1               5
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Arg Glu Thr Ile Glu Ser Thr Val
1               5
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Gln Asn Phe Arg Thr Tyr Ile Val Ser Phe Val
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Ser Asp Ser Asn Met Asn Met Asn Glu Leu Ser Glu Val
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Pro Pro Thr Cys Ser Gln Ala Asn Ser Gly Arg Ile Ser Thr Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Ile Asp Leu Ala Ser Glu Phe Leu Phe Leu Ser Asn Ser Phe Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asp Ser Glu Met Tyr Asn Phe Arg Ser Gln Leu Ala Ser Val Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Ile Pro Pro Asp Ser Glu Asp Gly Asn Glu Glu Gln Ser Leu Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Gln Ser Leu Val
1

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Ile Gln Ser Leu Val
1 5

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Glu Ile Gln Ser Leu Val
1 5

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Asn Glu Ile Gln Ser Leu Val
1 5

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Arg Asn Glu Ile Gln Ser Leu Val
1               5
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
1               5                   10                  15
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 427 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu
1               5                   10                  15

Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys
            20                  25                  30

Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn
        35                  40                  45

Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys
    50                  55                  60

Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr
65                  70                  75                  80

Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser
                85                  90                  95

Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly
            100                 105                 110

Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys
        115                 120                 125

Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr
    130                 135                 140

Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His
145                 150                 155                 160

Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln
                165                 170                 175

Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro
            180                 185                 190
```

Gly Arg Trp Ile Thr Arg Ser Thr Pro Pro Glu Gly Ser Asp Ser Thr
195 200 205

Ala Pro Ser Thr Gln Glu Pro Glu Ala Pro Pro Glu Gln Asp Leu Ile
210 215 220

Ala Ser Thr Val Ala Gly Val Val Thr Thr Val Met Gly Ser Ser Gln
225 230 235 240

Pro Val Val Thr Arg Gly Thr Thr Asp Asn Leu Ile Pro Val Tyr Cys
245 250 255

Ser Ile Leu Ala Ala Val Val Val Gly Leu Val Ala Tyr Ile Ala Phe
260 265 270

Lys Arg Trp Asn Ser Cys Lys Gln Asn Lys Gly Gly Ala Asn Ser Arg
275 280 285

Pro Val Asn Gln Thr Pro Pro Pro Glu Gly Glu Lys Ile His Ser Asp
290 295 300

Ser Gly Ile Ser Val Asp Ser Gln Ser Leu His Asp Gln Gln Pro His
305 310 315 320

Thr Gln Thr Ala Ser Gly Gln Ala Leu Lys Gly Asp Gly Gly Leu Tyr
325 330 335

Ser Ser Leu Pro Pro Ala Lys Arg Glu Glu Val Glu Lys Leu Leu Asn
340 345 350

Gly Ser Ala Gly Asp Thr Trp Arg His Leu Ala Gly Glu Leu Gly Tyr
355 360 365

Gln Pro Glu His Ile Asp Ser Phe Thr His Glu Ala Cys Pro Val Arg
370 375 380

Ala Leu Leu Ala Ser Trp Ala Thr Gln Asp Ser Ala Thr Leu Asp Ala
385 390 395 400

Leu Leu Ala Ala Leu Arg Arg Ile Gln Arg Ala Asp Leu Val Glu Ser
405 410 415

Leu Cys Ser Glu Ser Thr Ala Thr Ser Pro Val
420 425

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 458 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Asn Arg Gly Val Pro Phe Arg His Leu Leu Leu Val Leu Gln Leu
1 5 10 15

Ala Leu Leu Pro Ala Ala Thr Gln Gly Lys Lys Val Val Leu Gly Lys
20 25 30

Lys Gly Asp Thr Val Glu Leu Thr Cys Thr Ala Ser Gln Lys Lys Ser
35 40 45

```
Ile Gln Phe His Trp Lys Asn Ser Asn Gln Ile Lys Ile Leu Gly Asn
    50                  55                  60

Gln Gly Ser Phe Leu Thr Lys Gly Pro Ser Lys Leu Asn Asp Arg Ala
65                  70                  75                  80

Asp Ser Arg Arg Ser Leu Trp Asp Gln Gly Asn Phe Pro Leu Ile Ile
                85                  90                  95

Lys Asn Leu Lys Ile Glu Asp Ser Asp Thr Tyr Ile Cys Glu Val Glu
            100                 105                 110

Asp Gln Lys Glu Glu Val Gln Leu Leu Val Phe Gly Leu Thr Ala Asn
        115                 120                 125

Ser Asp Thr His Leu Leu Gln Gly Gln Ser Leu Thr Ile Thr Leu Glu
    130                 135                 140

Ser Pro Pro Gly Ser Ser Pro Ser Val Gln Cys Arg Ser Pro Arg Gly
145                 150                 155                 160

Lys Asn Ile Gln Gly Gly Lys Thr Leu Ser Val Ser Gln Leu Glu Leu
                165                 170                 175

Gln Asp Ser Gly Thr Trp Thr Cys Thr Val Leu Gln Asn Gln Lys Lys
            180                 185                 190

Val Glu Phe Lys Ile Asp Ile Val Val Leu Ala Phe Gln Lys Ala Ser
        195                 200                 205

Ser Ile Val Tyr Lys Lys Glu Gly Glu Gln Val Glu Phe Ser Phe Pro
    210                 215                 220

Leu Ala Phe Thr Val Glu Lys Leu Thr Gly Ser Gly Glu Leu Trp Trp
225                 230                 235                 240

Gln Ala Glu Arg Ala Ser Ser Ser Lys Ser Trp Ile Thr Phe Asp Leu
                245                 250                 255

Lys Asn Lys Glu Val Ser Val Lys Arg Val Thr Gln Asp Pro Lys Leu
            260                 265                 270

Gln Met Gly Lys Lys Leu Pro Leu His Leu Thr Leu Pro Gln Ala Leu
        275                 280                 285

Pro Gln Tyr Ala Gly Ser Gly Asn Leu Thr Leu Ala Leu Glu Ala Lys
    290                 295                 300

Thr Gly Lys Leu His Gln Glu Asn Val Leu Val Val Met Arg Ala Thr
305                 310                 315                 320

Gln Leu Gln Lys Asn Leu Thr Cys Glu Val Trp Gly Pro Thr Ser Pro
                325                 330                 335

Lys Leu Met Leu Ser Leu Lys Leu Glu Asn Lys Glu Ala Lys Val Ser
            340                 345                 350

Lys Arg Glu Lys Ala Val Trp Val Leu Asn Pro Glu Ala Gly Met Trp
        355                 360                 365

Gln Cys Leu Leu Ser Asp Ser Gly Gln Val Leu Leu Glu Ser Asn Ile
    370                 375                 380

Lys Val Leu Pro Thr Trp Ser Thr Pro Val Gln Pro Met Ala Leu Ile
385                 390                 395                 400

Val Leu Gly Gly Val Ala Gly Leu Leu Leu Phe Ile Gly Leu Gly Ile
```

405 410 415
Phe Phe Cys Val Arg Cys Arg His Arg Arg Arg Gln Ala Glu Arg Met
420 425 430
Ser Gln Ile Lys Arg Leu Leu Ser Glu Lys Lys Glu Cys Gln Cys Pro
435 440 445
His Arg Phe Gln Lys Thr Cys Ser Pro Ile
450 455

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 828 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Asn Ser Gly Val Ala Met Lys Tyr Gly Asn Asp Ser Ser Ala Glu
1 5 10 15
Leu Ser Glu Leu His Ser Ala Ala Leu Ala Ser Leu Lys Gly Asp Ile
20 25 30
Val Glu Leu Asn Lys Arg Leu Gln Gln Thr Glu Arg Glu Asp Leu Leu
35 40 45
Glu Lys Lys Leu Ala Lys Ala Gln Cys Glu Gln Ser His Leu Met Arg
50 55 60
Glu His Glu Asp Val Gln Glu Arg Thr Thr Leu Arg Tyr Glu Glu Arg
65 70 75 80
Ile Thr Glu Leu His Ser Val Ile Ala Glu Leu Asn Lys Lys Ile Asp
85 90 95
Arg Leu Gln Gly Thr Thr Ile Arg Glu Glu Asp Glu Tyr Ser Glu Leu
100 105 110
Arg Ser Glu Leu Ser Gln Ser Gln His Glu Val Asn Glu Asp Ser Arg
115 120 125
Ser Met Asp Gln Asp Gln Thr Ser Val Ser Ile Pro Glu Asn Gln Ser
130 135 140
Thr Met Val Thr Ala Asp Met Asp Asn Cys Ser Asp Ile Asn Ser Glu
145 150 155 160
Leu Gln Arg Val Leu Thr Gly Leu Glu Asn Val Val Cys Gly Arg Lys
165 170 175
Lys Ser Ser Cys Ser Leu Ser Val Ala Glu Val Asp Arg His Ile Glu
180 185 190
Gln Leu Thr Thr Ala Ser Glu His Cys Asp Leu Ala Ile Lys Thr Val
195 200 205
Glu Glu Ile Glu Gly Val Leu Gly Arg Asp Leu Tyr Pro Asn Leu Ala
210 215 220
Glu Glu Arg Ser Arg Trp Glu Lys Glu Leu Ala Gly Leu Arg Glu Glu

225 230 235 240

Asn Glu Ser Leu Thr Ala Met Leu Cys Ser Lys Glu Glu Glu Leu Asn
245 250 255

Arg Thr Lys Ala Thr Met Asn Ala Ile Arg Glu Glu Arg Asp Arg Leu
260 265 270

Arg Arg Arg Val Arg Glu Leu Gln Thr Arg Leu Gln Ser Val Gln Ala
275 280 285

Thr Gly Pro Ser Ser Pro Gly Arg Leu Thr Ser Thr Asn Arg Pro Ile
290 295 300

Asn Pro Ser Thr Gly Glu Leu Ser Thr Ser Ser Ser Ser Asn Asp Ile
305 310 315 320

Pro Ile Ala Lys Ile Ala Glu Arg Val Lys Leu Ser Lys Thr Arg Ser
325 330 335

Glu Ser Ser Ser Ser Asp Arg Pro Val Leu Gly Ser Glu Ile Ser Ser
340 345 350

Ile Gly Val Ser Ser Ser Val Ala Glu His Leu Ala His Ser Leu Gln
355 360 365

Asp Cys Ser Asn Ile Gln Glu Ile Phe Gln Thr Leu Tyr Ser His Gly
370 375 380

Ser Ala Ile Ser Glu Ser Lys Ile Arg Glu Phe Glu Val Glu Thr Glu
385 390 395 400

Arg Leu Asn Ser Arg Ile Glu His Leu Lys Ser Gln Asn Asp Leu Leu
405 410 415

Thr Ile Thr Leu Glu Glu Cys Lys Ser Asn Ala Glu Arg Met Ser Met
420 425 430

Leu Val Gly Lys Tyr Glu Ser Asn Ala Thr Ala Leu Arg Leu Ala Leu
435 440 445

Gln Tyr Ser Glu Gln Cys Ile Glu Ala Tyr Glu Leu Leu Leu Ala Leu
450 455 460

Ala Glu Ser Glu Gln Ser Leu Ile Leu Gly Gln Phe Arg Ala Ala Gly
465 470 475 480

Val Gly Ser Ser Pro Gly Asp Gln Ser Gly Asp Glu Asn Ile Thr Gln
485 490 495

Met Leu Lys Arg Ala His Asp Cys Arg Lys Thr Ala Glu Asn Ala Ala
500 505 510

Lys Ala Leu Leu Met Lys Leu Asp Gly Ser Cys Gly Gly Ala Phe Ala
515 520 525

Val Ala Gly Cys Ser Val Gln Pro Trp Glu Ser Leu Ser Ser Asn Ser
530 535 540

His Thr Ser Thr Thr Ser Ser Thr Ala Ser Ser Cys Asp Thr Glu Phe
545 550 555 560

Thr Lys Glu Asp Glu Gln Arg Leu Lys Asp Tyr Ile Gln Gln Leu Lys
565 570 575

Asn Asp Arg Ala Ala Val Lys Leu Thr Met Leu Glu Leu Glu Ser Ile
580 585 590

His Ile Asp Pro Leu Ser Tyr Asp Val Lys Pro Arg Gly Asp Ser Gln
595 600 605

Arg Leu Asp Leu Glu Asn Ala Val Leu Met Gln Glu Leu Met Ala Met
610 615 620

Lys Glu Glu Met Ala Glu Leu Lys Ala Gln Leu Tyr Leu Leu Glu Lys
625 630 635 640

Glu Lys Lys Ala Leu Glu Leu Lys Leu Ser Thr Arg Glu Ala Gln Glu
645 650 655

Gln Ala Tyr Leu Val His Ile Glu His Leu Lys Ser Glu Val Glu Glu
660 665 670

Gln Lys Glu Gln Arg Met Arg Ser Leu Ser Ser Thr Ser Ser Gly Ser
675 680 685

Lys Asp Lys Pro Gly Lys Glu Cys Ala Asp Ala Ala Ser Pro Ala Leu
690 695 700

Ser Leu Ala Glu Leu Arg Thr Thr Cys Ser Glu Asn Glu Leu Ala Ala
705 710 715 720

Glu Phe Thr Asn Ala Ile Arg Arg Glu Lys Lys Leu Lys Ala Arg Val
725 730 735

Gln Glu Leu Val Ser Ala Leu Glu Arg Leu Thr Lys Ser Ser Glu Ile
740 745 750

Arg His Gln Gln Ser Ala Glu Phe Val Asn Asp Leu Lys Arg Ala Asn
755 760 765

Ser Asn Leu Val Ala Ala Tyr Glu Lys Ala Lys Lys Lys His Gln Asn
770 775 780

Lys Leu Lys Lys Leu Glu Ser Gln Met Met Ala Met Val Glu Arg His
785 790 795 800

Glu Thr Gln Val Arg Met Leu Lys Gln Arg Ile Ala Leu Leu Glu Glu
805 810 815

Glu Asn Ser Arg Pro His Thr Asn Glu Thr Ser Leu
820 825

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 672 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Ala Asp Val Phe Pro Gly Asn Asp Ser Thr Ala Ser Gln Asp Val
1 5 10 15

Ala Asn Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His
20 25 30

Glu Val Lys Asp His Lys Phe Ile Ala Arg Phe Phe Lys Gln Pro Thr
35 40 45

```
Phe Cys Ser His Cys Thr Asp Phe Ile Trp Gly Phe Gly Lys Gly Gly
    50                  55                  60

Phe Gln Cys Gln Val Cys Cys Phe Val Val His Lys Arg Cys His Glu
65                  70                  75                  80

Phe Val Thr Phe Ser Cys Pro Gly Ala Asp Lys Gly Pro Asp Thr Asp
                85                  90                  95

Asp Pro Arg Ser Lys His Lys Phe Lys Ile His Thr Tyr Gly Ser Pro
            100                 105                 110

Thr Phe Cys Asp His Cys Gly Ser Leu Leu Tyr Gly Leu Ile His Gln
        115                 120                 125

Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Lys Gln Cys Val
    130                 135                 140

Ile Asn Val Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly
145                 150                 155                 160

Arg Ile Tyr Leu Lys Ala Glu Val Ala Asp Glu Lys Leu His Val Thr
                165                 170                 175

Val Arg Asp Ala Lys Asn Leu Ile Pro Met Asp Pro Asn Gly Leu Ser
            180                 185                 190

Asp Pro Tyr Val Lys Leu Lys Leu Ile Pro Asp Pro Lys Asn Glu Ser
        195                 200                 205

Lys Gln Lys Thr Lys Thr Ile Arg Ser Thr Leu Asn Pro Gln Trp Asn
    210                 215                 220

Glu Ser Phe Thr Phe Lys Leu Lys Pro Ser Asp Lys Asp Arg Arg Leu
225                 230                 235                 240

Ser Val Glu Ile Trp Asp Trp Asp Arg Thr Thr Arg Asn Asp Phe Met
                245                 250                 255

Gly Ser Leu Ser Phe Gly Val Ser Glu Leu Met Lys Met Pro Ala Ser
            260                 265                 270

Gly Trp Tyr Lys Leu Leu Asn Gln Glu Glu Gly Glu Tyr Tyr Asn Val
        275                 280                 285

Pro Ile Pro Glu Gly Asp Glu Glu Gly Asn Met Glu Leu Arg Gln Lys
    290                 295                 300

Phe Glu Lys Ala Lys Leu Gly Pro Ala Gly Asn Lys Val Ile Ser Pro
305                 310                 315                 320

Ser Glu Asp Arg Lys Gln Pro Ser Asn Asn Leu Asp Arg Val Lys Leu
                325                 330                 335

Thr Asp Phe Asn Phe Leu Met Val Leu Gly Lys Gly Ser Phe Gly Lys
            340                 345                 350

Val Met Leu Ala Asp Arg Lys Gly Thr Glu Glu Leu Tyr Ala Ile Lys
        355                 360                 365

Ile Leu Lys Lys Asp Val Val Ile Gln Asp Asp Asp Val Glu Cys Thr
    370                 375                 380

Met Val Glu Lys Arg Val Leu Ala Leu Leu Asp Lys Pro Pro Phe Leu
385                 390                 395                 400

Thr Gln Leu His Ser Cys Phe Gln Thr Val Asp Arg Leu Tyr Phe Val
```

```
                    405                     410                     415

Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile Gln Gln Val
            420                     425                     430

Gly Lys Phe Lys Glu Pro Gln Ala Val Phe Tyr Ala Ala Glu Ile Ser
        435                     440                     445

Ile Gly Leu Phe Phe Leu His Lys Arg Gly Ile Ile Tyr Arg Asp Leu
    450                     455                     460

Lys Leu Asp Asn Val Met Leu Asp Ser Glu Gly His Ile Lys Ile Ala
465                     470                     475                 480

Asp Phe Gly Met Cys Lys Glu His Met Met Asp Gly Val Thr Thr Arg
                485                     490                     495

Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile Ile Ala Tyr
            500                     505                     510

Gln Pro Tyr Gly Lys Ser Val Asp Trp Trp Ala Tyr Gly Val Leu Leu
        515                     520                     525

Tyr Glu Met Leu Ala Gly Gln Pro Pro Phe Asp Gly Glu Asp Glu Asp
    530                     535                     540

Glu Leu Phe Gln Ser Ile Met Glu His Asn Val Ser Tyr Pro Lys Ser
545                     550                     555                 560

Leu Ser Lys Glu Ala Val Ser Ile Cys Lys Gly Leu Met Thr Lys His
                565                     570                     575

Pro Ala Lys Arg Leu Gly Cys Gly Pro Glu Gly Glu Arg Asp Val Arg
            580                     585                     590

Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg
        595                     600                     605

Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu
    610                     615                     620

Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro
625                     630                     635                 640

Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe
                645                     650                     655

Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val
            660                     665                     670
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 471 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Asp Ile Leu Cys Glu Glu Asn Thr Ser Leu Ser Ser Thr Thr Asn
1               5                   10                  15
```

```
Ser Leu Met Gln Leu Asn Asp Asp Thr Arg Leu Tyr Ser Asn Asp Phe
            20                  25                  30

Asn Ser Gly Glu Ala Asn Thr Ser Asp Ala Phe Asn Trp Thr Val Asp
        35                  40                  45

Ser Glu Asn Arg Thr Asn Leu Ser Cys Glu Gly Cys Leu Ser Pro Ser
    50                  55                  60

Cys Leu Ser Leu Leu His Leu Gln Glu Lys Asn Trp Ser Ala Leu Leu
65                  70                  75                  80

Thr Ala Val Val Ile Ile Leu Thr Ile Ala Gly Asn Ile Leu Val Ile
                85                  90                  95

Met Ala Val Ser Leu Glu Lys Lys Leu Gln Asn Ala Thr Asn Tyr Phe
            100                 105                 110

Leu Met Ser Leu Ala Ile Ala Asp Met Leu Leu Gly Phe Leu Val Met
        115                 120                 125

Pro Val Ser Met Leu Thr Ile Leu Tyr Gly Tyr Arg Trp Pro Leu Pro
    130                 135                 140

Ser Lys Leu Cys Ala Val Trp Ile Tyr Leu Asp Val Leu Phe Ser Thr
145                 150                 155                 160

Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala
                165                 170                 175

Ile Gln Asn Pro Ile His His Ser Arg Phe Asn Ser Arg Thr Lys Ala
            180                 185                 190

Phe Leu Lys Ile Ile Ala Val Trp Thr Ile Ser Val Gly Ile Ser Met
        195                 200                 205

Pro Ile Pro Val Phe Gly Leu Gln Asp Asp Ser Lys Val Phe Lys Glu
    210                 215                 220

Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe Val Leu Ile Gly Ser Phe
225                 230                 235                 240

Val Ser Phe Phe Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Phe Leu
                245                 250                 255

Thr Ile Lys Ser Leu Gln Lys Glu Ala Thr Leu Cys Val Ser Asp Leu
            260                 265                 270

Gly Thr Arg Ala Lys Leu Ala Ser Phe Ser Phe Leu Pro Gln Ser Ser
        275                 280                 285

Leu Ser Ser Glu Lys Leu Phe Gln Arg Ser Ile His Arg Glu Pro Gly
    290                 295                 300

Ser Tyr Thr Gly Arg Arg Thr Met Gln Ser Ile Ser Asn Glu Gln Lys
305                 310                 315                 320

Ala Cys Lys Val Leu Gly Ile Val Phe Phe Leu Phe Val Val Met Trp
                325                 330                 335

Cys Pro Phe Phe Ile Thr Asn Ile Met Ala Val Ile Cys Lys Glu Ser
            340                 345                 350

Cys Asn Glu Asp Val Ile Gly Ala Leu Leu Asn Val Phe Val Trp Ile
        355                 360                 365

Gly Tyr Leu Ser Ser Ala Val Asn Pro Leu Val Tyr Thr Leu Phe Asn
```

370 375 380

Lys Thr Tyr Arg Ser Ala Phe Ser Arg Tyr Ile Gln Cys Gln Tyr Lys
385 390 395 400

Glu Asn Lys Lys Pro Leu Gln Leu Ile Leu Val Asn Thr Ile Pro Ala
405 410 415

Leu Ala Tyr Lys Ser Ser Gln Leu Gln Met Gly Gln Lys Lys Asn Ser
420 425 430

Lys Gln Asp Ala Lys Thr Thr Asp Asn Asp Cys Ser Met Val Ala Leu
435 440 445

Gly Lys Gln His Ser Glu Glu Ala Ser Lys Asp Asn Ser Asp Gly Val
450 455 460

Asn Glu Lys Val Ser Cys Val
465 470

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met Ala Leu Ser Tyr Arg Val Ser Glu Leu Gln Ser Thr Ile Pro Glu
1 5 10 15

His Ile Leu Gln Ser Thr Phe Val His Val Ile Ser Ser Asn Trp Ser
20 25 30

Gly Leu Gln Thr Glu Ser Ile Pro Glu Glu Met Lys Gln Ile Val Glu
35 40 45

Glu Gln Gly Asn Lys Leu His Trp Ala Ala Leu Leu Ile Leu Met Val
50 55 60

Ile Ile Pro Thr Ile Gly Gly Asn Thr Leu Val Ile Leu Ala Val Ser
65 70 75 80

Leu Glu Lys Lys Leu Gln Tyr Ala Thr Asn Tyr Phe Leu Met Ser Leu
85 90 95

Ala Val Ala Asp Leu Leu Val Gly Leu Phe Val Met Pro Ile Ala Leu
100 105 110

Leu Thr Ile Met Phe Glu Ala Met Trp Pro Leu Pro Leu Val Leu Cys
115 120 125

Pro Ala Trp Leu Phe Leu Asp Val Leu Phe Ser Thr Ala Ser Ile Met
130 135 140

His Leu Cys Ala Ile Ser Val Asp Arg Tyr Ile Ala Ile Lys Lys Pro
145 150 155 160

Ile Gln Ala Asn Gln Tyr Asn Ser Arg Ala Thr Ala Phe Ile Lys Ile
165 170 175

Thr Val Val Trp Leu Ile Ser Ile Gly Ile Ala Ile Pro Val Pro Ile

```
            180                     185                     190
Lys Gly Ile Glu Thr Asp Val Asp Asn Pro Asn Asn Ile Thr Cys Val
        195                     200                     205

Leu Thr Lys Glu Arg Phe Gly Asp Phe Met Leu Phe Gly Ser Leu Ala
    210                     215                     220

Ala Phe Phe Thr Pro Leu Ala Ile Met Ile Val Thr Tyr Phe Leu Thr
225                     230                     235                 240

Ile His Ala Leu Gln Lys Lys Ala Tyr Leu Val Lys Asn Lys Pro Pro
                245                     250                     255

Gln Arg Leu Thr Trp Leu Thr Val Ser Thr Val Phe Gln Arg Asp Glu
            260                     265                     270

Thr Pro Cys Ser Ser Pro Glu Lys Val Ala Met Leu Asp Gly Ser Arg
        275                     280                     285

Lys Asp Lys Ala Leu Pro Asn Ser Gly Asp Glu Thr Leu Met Arg Arg
    290                     295                     300

Thr Ser Thr Ile Gly Lys Lys Ser Val Gln Thr Ile Ser Asn Glu Gln
305                     310                     315                 320

Arg Ala Ser Lys Val Leu Gly Ile Val Phe Phe Leu Phe Leu Leu Met
                325                     330                     335

Trp Cys Pro Phe Phe Ile Thr Asn Ile Thr Leu Val Leu Cys Asp Ser
            340                     345                     350

Cys Asn Gln Thr Thr Leu Gln Met Leu Leu Glu Ile Phe Val Trp Ile
        355                     360                     365

Gly Tyr Val Ser Ser Gly Val Asn Pro Leu Val Tyr Thr Leu Phe Asn
    370                     375                     380

Lys Thr Phe Arg Asp Ala Phe Gly Arg Tyr Ile Thr Cys Asn Tyr Arg
385                     390                     395                 400

Ala Thr Lys Ser Val Lys Thr Leu Arg Lys Arg Ser Ser Lys Ile Tyr
                405                     410                     415

Phe Arg Asn Pro Met Ala Glu Asn Ser Lys Phe Phe Lys Lys His Gly
            420                     425                     430

Ile Arg Asn Gly Ile Asn Pro Ala Met Tyr Gln Ser Pro Met Arg Leu
        435                     440                     445

Arg Ser Ser Thr Ile Gln Ser Ser Ser Ile Ile Leu Leu Asp Thr Leu
    450                     455                     460

Leu Leu Thr Glu Asn Glu Gly Asp Lys Thr Glu Glu Gln Val Ser Val
465                     470                     475                 480

Val
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2843 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Ala Ala Ala Ser Tyr Asp Gln Leu Leu Lys Gln Val Glu Ala Leu
1   5   10   15

Lys Met Glu Asn Ser Asn Leu Arg Gln Glu Leu Glu Asp Asn Ser Asn
            20   25   30

His Leu Thr Lys Leu Glu Thr Glu Ala Ser Asn Met Lys Glu Val Leu
        35   40   45

Lys Gln Leu Gln Gly Ser Ile Glu Asp Glu Ala Met Ala Ser Ser Gly
    50   55   60

Gln Ile Asp Leu Leu Glu Arg Leu Lys Glu Leu Asn Leu Asp Ser Ser
65   70   75   80

Asn Phe Pro Gly Val Lys Leu Arg Ser Lys Met Ser Leu Arg Ser Tyr
                85   90   95

Gly Ser Arg Glu Gly Ser Val Ser Ser Arg Ser Gly Glu Cys Ser Pro
            100   105   110

Val Pro Met Gly Ser Phe Pro Arg Arg Gly Phe Val Asn Gly Ser Arg
        115   120   125

Glu Ser Thr Gly Tyr Leu Glu Glu Leu Glu Lys Glu Arg Ser Leu Leu
    130   135   140

Leu Ala Asp Leu Asp Lys Glu Glu Lys Glu Lys Asp Trp Tyr Tyr Ala
145   150   155   160

Gln Leu Gln Asn Leu Thr Lys Arg Ile Asp Ser Leu Pro Leu Thr Glu
                165   170   175

Asn Phe Ser Leu Gln Thr Asp Met Thr Arg Arg Gln Leu Glu Tyr Glu
            180   185   190

Ala Arg Gln Ile Arg Val Ala Met Glu Glu Gln Leu Gly Thr Cys Gln
        195   200   205

Asp Met Glu Lys Arg Ala Gln Arg Arg Ile Ala Arg Ile Gln Gln Ile
    210   215   220

Glu Lys Asp Ile Leu Arg Ile Arg Gln Leu Leu Gln Ser Gln Ala Thr
225   230   235   240

Glu Ala Glu Arg Ser Ser Gln Asn Lys His Glu Thr Gly Ser His Asp
                245   250   255

Ala Glu Arg Gln Asn Glu Gly Gln Gly Val Gly Glu Ile Asn Met Ala
            260   265   270

Thr Ser Gly Asn Gly Gln Gly Ser Thr Thr Arg Met Asp His Glu Thr
        275   280   285

Ala Ser Val Leu Ser Ser Ser Ser Thr His Ser Ala Pro Arg Arg Leu
    290   295   300

Thr Ser His Leu Gly Thr Lys Val Glu Met Val Tyr Ser Leu Leu Ser
305   310   315   320

Met Leu Gly Thr His Asp Lys Asp Asp Met Ser Arg Thr Leu Leu Ala
                325   330   335

Met Ser Ser Ser Gln Asp Ser Cys Ile Ser Met Arg Gln Ser Gly Cys
340 345 350

Leu Pro Leu Leu Ile Gln Leu Leu His Gly Asn Asp Lys Asp Ser Val
355 360 365

Leu Leu Gly Asn Ser Arg Gly Ser Lys Glu Ala Arg Ala Arg Ala Ser
370 375 380

Ala Ala Leu His Asn Ile Ile His Ser Gln Pro Asp Asp Lys Arg Gly
385 390 395 400

Arg Arg Glu Ile Arg Val Leu His Leu Leu Glu Gln Ile Arg Ala Tyr
405 410 415

Cys Ser Thr Cys Trp Glu Trp Gln Glu Ala His Glu Pro Gly Met Asp
420 425 430

Gln Asp Lys Asn Pro Met Pro Ala Pro Val Glu His Gln Ile Cys Pro
435 440 445

Ala Val Cys Val Leu Met Lys Leu Ser Phe Asp Glu Glu His Arg His
450 455 460

Ala Met Asn Glu Leu Gly Gly Leu Gln Ala Ile Ala Glu Leu Leu Gln
465 470 475 480

Val Asp Cys Glu Met Tyr Gly Leu Thr Asn Asp His Tyr Ser Ile Thr
485 490 495

Leu Arg Arg Tyr Ala Gly Met Ala Leu Thr Asn Leu Thr Phe Gly Asp
500 505 510

Val Ala Asn Lys Ala Thr Leu Cys Ser Met Lys Gly Cys Met Arg Ala
515 520 525

Leu Val Ala Gln Leu Lys Ser Glu Ser Glu Asp Leu Gln Gln Val Ile
530 535 540

Ala Ser Val Leu Arg Asn Leu Ser Trp Arg Ala Asp Val Asn Ser Lys
545 550 555 560

Lys Thr Leu Arg Glu Val Gly Ser Val Lys Ala Leu Met Glu Cys Ala
565 570 575

Leu Glu Val Lys Lys Glu Ser Thr Leu Lys Ser Val Leu Ser Ala Leu
580 585 590

Trp Asn Leu Ser Ala His Cys Thr Glu Asn Lys Ala Asp Ile Cys Ala
595 600 605

Val Asp Gly Ala Leu Ala Phe Leu Val Gly Thr Leu Thr Tyr Arg Ser
610 615 620

Gln Thr Asn Thr Leu Ala Ile Ile Glu Ser Gly Gly Gly Ile Leu Arg
625 630 635 640

Asn Val Ser Ser Leu Ile Ala Thr Asn Glu Asp His Arg Gln Ile Leu
645 650 655

Arg Glu Asn Asn Cys Leu Gln Thr Leu Leu Gln His Leu Lys Ser His
660 665 670

Ser Leu Thr Ile Val Ser Asn Ala Cys Gly Thr Leu Trp Asn Leu Ser
675 680 685

Ala Arg Asn Pro Lys Asp Gln Glu Ala Leu Trp Asp Met Gly Ala Val

690 695 700

Ser Met Leu Lys Asn Leu Ile His Ser Lys His Lys Met Ile Ala Met
705 710 715 720

Gly Ser Ala Ala Ala Leu Arg Asn Leu Met Ala Asn Arg Pro Ala Lys
725 730 735

Tyr Lys Asp Ala Asn Ile Met Ser Pro Gly Ser Ser Leu Pro Ser Leu
740 745 750

His Val Arg Lys Gln Lys Ala Leu Glu Ala Glu Leu Asp Ala Gln His
755 760 765

Leu Ser Glu Thr Phe Asp Asn Ile Asp Asn Ile Ser Pro Lys Ala Ser
770 775 780

His Arg Ser Lys Gln Arg His Lys Gln Ser Leu Tyr Gly Asp Tyr Val
785 790 795 800

Phe Asp Thr Asn Arg His Asp Asp Asn Arg Ser Asp Asn Phe Asn Thr
805 810 815

Gly Asn Met Thr Val Leu Ser Pro Tyr Leu Asn Thr Thr Val Leu Pro
820 825 830

Ser Ser Ser Ser Ser Arg Gly Ser Leu Asp Ser Ser Arg Ser Glu Lys
835 840 845

Asp Arg Ser Leu Glu Arg Glu Arg Gly Ile Gly Leu Gly Asn Tyr His
850 855 860

Pro Ala Thr Glu Asn Pro Gly Thr Ser Ser Lys Arg Gly Leu Gln Ile
865 870 875 880

Ser Thr Thr Ala Ala Gln Ile Ala Lys Val Met Glu Glu Val Ser Ala
885 890 895

Ile His Thr Ser Gln Glu Asp Arg Ser Ser Gly Ser Thr Thr Glu Leu
900 905 910

His Cys Val Thr Asp Glu Arg Asn Ala Leu Arg Arg Ser Ser Ala Ala
915 920 925

His Thr His Ser Asn Thr Tyr Asn Phe Thr Lys Ser Glu Asn Ser Asn
930 935 940

Arg Thr Cys Ser Met Pro Tyr Ala Lys Leu Glu Tyr Lys Arg Ser Ser
945 950 955 960

Asn Asp Ser Leu Asn Ser Val Ser Ser Ser Asp Gly Tyr Gly Lys Arg
965 970 975

Gly Gln Met Lys Pro Ser Ile Glu Ser Tyr Ser Glu Asp Asp Glu Ser
980 985 990

Lys Phe Cys Ser Tyr Gly Gln Tyr Pro Ala Asp Leu Ala His Lys Ile
995 1000 1005

His Ser Ala Asn His Met Asp Asp Asn Asp Gly Glu Leu Asp Thr Pro
1010 1015 1020

Ile Asn Tyr Ser Leu Lys Tyr Ser Asp Glu Gln Leu Asn Ser Gly Arg
1025 1030 1035 1040

Gln Ser Pro Ser Gln Asn Glu Arg Trp Ala Arg Pro Lys His Ile Ile
1045 1050 1055

Glu Asp Glu Ile Lys Gln Ser Glu Gln Arg Gln Ser Arg Asn Gln Ser
1060 1065 1070

Thr Thr Tyr Pro Val Tyr Thr Glu Ser Thr Asp Asp Lys His Leu Lys
1075 1080 1085

Phe Gln Pro His Phe Gly Gln Gln Glu Cys Val Ser Pro Tyr Arg Ser
1090 1095 1100

Arg Gly Ala Asn Gly Ser Glu Thr Asn Arg Val Gly Ser Asn His Gly
1105 1110 1115 1120

Ile Asn Gln Asn Val Ser Gln Ser Leu Cys Gln Glu Asp Asp Tyr Glu
1125 1130 1135

Asp Asp Lys Pro Thr Asn Tyr Ser Glu Arg Tyr Ser Glu Glu Glu Gln
1140 1145 1150

His Glu Glu Glu Glu Arg Pro Thr Asn Tyr Ser Ile Lys Tyr Asn Glu
1155 1160 1165

Glu Lys Arg His Val Asp Gln Pro Ile Asp Tyr Ser Ile Leu Lys Ala
1170 1175 1180

Thr Asp Ile Pro Ser Ser Gln Lys Gln Ser Phe Ser Phe Ser Lys Ser
1185 1190 1195 1200

Ser Ser Gly Gln Ser Ser Lys Thr Glu His Met Ser Ser Ser Ser Glu
1205 1210 1215

Asn Thr Ser Thr Pro Ser Ser Asn Ala Lys Arg Gln Asn Gln Leu His
1220 1225 1230

Pro Ser Ser Ala Gln Ser Arg Ser Gly Gln Pro Gln Lys Ala Ala Thr
1235 1240 1245

Cys Lys Val Ser Ser Ile Asn Gln Glu Thr Ile Gln Thr Tyr Cys Val
1250 1255 1260

Glu Asp Thr Pro Ile Cys Phe Ser Arg Cys Ser Ser Leu Ser Ser Leu
1265 1270 1275 1280

Ser Ser Ala Glu Asp Glu Ile Gly Cys Asn Gln Thr Thr Gln Glu Ala
1285 1290 1295

Asp Ser Ala Asn Thr Leu Gln Ile Ala Glu Ile Lys Glu Lys Ile Gly
1300 1305 1310

Thr Arg Ser Ala Glu Asp Pro Val Ser Glu Val Pro Ala Val Ser Gln
1315 1320 1325

His Pro Arg Thr Lys Ser Ser Arg Leu Gln Gly Ser Ser Leu Ser Ser
1330 1335 1340

Glu Ser Ala Arg His Lys Ala Val Glu Phe Ser Ser Gly Ala Lys Ser
1345 1350 1355 1360

Pro Ser Lys Ser Gly Ala Gln Thr Pro Lys Ser Pro Pro Glu His Tyr
1365 1370 1375

Val Gln Glu Thr Pro Leu Met Phe Ser Arg Cys Thr Ser Val Ser Ser
1380 1385 1390

Leu Asp Ser Phe Glu Ser Arg Ser Ile Ala Ser Ser Val Gln Ser Glu
1395 1400 1405

Pro Cys Ser Gly Met Val Ser Gly Ile Ile Ser Pro Ser Asp Leu Pro

1410 1415 1420

Asp Ser Pro Gly Gln Thr Met Pro Pro Ser Arg Ser Lys Thr Pro Pro
1425 1430 1435 1440

Pro Pro Pro Gln Thr Ala Gln Thr Lys Arg Glu Val Pro Lys Asn Lys
1445 1450 1455

Ala Pro Thr Ala Glu Lys Arg Glu Ser Gly Pro Lys Gln Ala Ala Val
1460 1465 1470

Asn Ala Ala Val Gln Arg Val Gln Val Leu Pro Asp Ala Asp Thr Leu
1475 1480 1485

Leu His Phe Ala Thr Glu Ser Thr Pro Asp Gly Phe Ser Cys Ser Ser
1490 1495 1500

Ser Leu Ser Ala Leu Ser Leu Asp Glu Pro Phe Ile Gln Lys Asp Val
1505 1510 1515 1520

Glu Leu Arg Ile Met Pro Pro Val Gln Glu Asn Asp Asn Gly Asn Glu
1525 1530 1535

Thr Glu Ser Glu Gln Pro Lys Glu Ser Asn Glu Asn Gln Glu Lys Glu
1540 1545 1550

Ala Glu Lys Thr Ile Asp Ser Glu Lys Asp Leu Leu Asp Asp Ser Asp
1555 1560 1565

Asp Asp Asp Ile Glu Ile Leu Glu Glu Cys Ile Ile Ser Ala Met Pro
1570 1575 1580

Thr Lys Ser Ser Arg Lys Ala Lys Lys Pro Ala Gln Thr Ala Ser Lys
1585 1590 1595 1600

Leu Pro Pro Pro Val Ala Arg Lys Pro Ser Gln Leu Pro Val Tyr Lys
1605 1610 1615

Leu Leu Pro Ser Gln Asn Arg Leu Gln Pro Gln Lys His Val Ser Phe
1620 1625 1630

Thr Pro Gly Asp Asp Met Pro Arg Val Tyr Cys Val Glu Gly Thr Pro
1635 1640 1645

Ile Asn Phe Ser Thr Ala Thr Ser Leu Ser Asp Leu Thr Ile Glu Ser
1650 1655 1660

Pro Pro Asn Glu Leu Ala Ala Gly Glu Gly Val Arg Gly Gly Ala Gln
1665 1670 1675 1680

Ser Gly Glu Phe Glu Lys Arg Asp Thr Ile Pro Thr Glu Gly Arg Ser
1685 1690 1695

Thr Asp Glu Ala Gln Gly Gly Lys Thr Ser Ser Val Thr Ile Pro Glu
1700 1705 1710

Leu Asp Asp Asn Lys Ala Glu Glu Gly Asp Ile Leu Ala Glu Cys Ile
1715 1720 1725

Asn Ser Ala Met Pro Lys Gly Lys Ser His Lys Pro Phe Arg Val Lys
1730 1735 1740

Lys Ile Met Asp Gln Val Gln Gln Ala Ser Ala Ser Ser Ser Ala Pro
1745 1750 1755 1760

Asn Lys Asn Gln Leu Asp Gly Lys Lys Lys Lys Pro Thr Ser Pro Val
1765 1770 1775

Lys Pro Ile Pro Gln Asn Thr Glu Tyr Arg Thr Arg Val Arg Lys Asn
1780 1785 1790

Ala Asp Ser Lys Asn Asn Leu Asn Ala Glu Arg Val Phe Ser Asp Asn
1795 1800 1805

Lys Asp Ser Lys Lys Gln Asn Leu Lys Asn Asn Ser Lys Asp Phe Asn
1810 1815 1820

Asp Lys Leu Pro Asn Asn Glu Asp Arg Val Arg Gly Ser Phe Ala Phe
1825 1830 1835 1840

Asp Ser Pro His His Tyr Thr Pro Ile Glu Gly Thr Pro Tyr Cys Phe
1845 1850 1855

Ser Arg Asn Asp Ser Leu Ser Ser Leu Asp Phe Asp Asp Asp Asp Val
1860 1865 1870

Asp Leu Ser Arg Glu Lys Ala Glu Leu Arg Lys Ala Lys Glu Asn Lys
1875 1880 1885

Glu Ser Glu Ala Lys Val Thr Ser His Thr Glu Leu Thr Ser Asn Gln
1890 1895 1900

Gln Ser Ala Asn Lys Thr Gln Ala Ile Ala Lys Gln Pro Ile Asn Arg
1905 1910 1915 1920

Gly Gln Pro Lys Pro Ile Leu Gln Lys Gln Ser Thr Phe Pro Gln Ser
1925 1930 1935

Ser Lys Asp Ile Pro Asp Arg Gly Ala Ala Thr Asp Glu Lys Leu Gln
1940 1945 1950

Asn Phe Ala Ile Glu Asn Thr Pro Val Cys Phe Ser His Asn Ser Ser
1955 1960 1965

Leu Ser Ser Leu Ser Asp Ile Asp Gln Glu Asn Asn Asn Lys Glu Asn
1970 1975 1980

Glu Pro Ile Lys Glu Thr Glu Pro Pro Asp Ser Gln Gly Glu Pro Ser
1985 1990 1995 2000

Lys Pro Gln Ala Ser Gly Tyr Ala Pro Lys Ser Phe His Val Glu Asp
2005 2010 2015

Thr Pro Val Cys Phe Ser Arg Asn Ser Ser Leu Ser Ser Leu Ser Ile
2020 2025 2030

Asp Ser Glu Asp Asp Leu Leu Gln Glu Cys Ile Ser Ser Ala Met Pro
2035 2040 2045

Lys Lys Lys Lys Pro Ser Arg Leu Lys Gly Asp Asn Glu Lys His Ser
2050 2055 2060

Pro Arg Asn Met Gly Gly Ile Leu Gly Glu Asp Leu Thr Leu Asp Leu
2065 2070 2075 2080

Lys Asp Ile Gln Arg Pro Asp Ser Glu His Gly Leu Ser Pro Asp Ser
2085 2090 2095

Glu Asn Phe Asp Trp Lys Ala Ile Gln Glu Gly Ala Asn Ser Ile Val
2100 2105 2110

Ser Ser Leu His Gln Ala Ala Ala Ala Ala Cys Leu Ser Arg Gln Ala
2115 2120 2125

Ser Ser Asp Ser Asp Ser Ile Leu Ser Leu Lys Ser Gly Ile Ser Leu

2130 2135 2140

Gly Ser Pro Phe His Leu Thr Pro Asp Gln Glu Glu Lys Pro Phe Thr
2145 2150 2155 2160

Ser Asn Lys Gly Pro Arg Ile Leu Lys Pro Gly Glu Lys Ser Thr Leu
2165 2170 2175

Glu Thr Lys Lys Ile Glu Ser Glu Ser Lys Gly Ile Lys Gly Gly Lys
2180 2185 2190

Lys Val Tyr Lys Ser Leu Ile Thr Gly Lys Val Arg Ser Asn Ser Glu
2195 2200 2205

Ile Ser Gly Gln Met Lys Gln Pro Leu Gln Ala Asn Met Pro Ser Ile
2210 2215 2220

Ser Arg Gly Arg Thr Met Ile His Ile Pro Gly Val Arg Asn Ser Ser
2225 2230 2235 2240

Ser Ser Thr Ser Pro Val Ser Lys Lys Gly Pro Pro Leu Lys Thr Pro
2245 2250 2255

Ala Ser Lys Ser Pro Ser Glu Gly Gln Thr Ala Thr Thr Ser Pro Arg
2260 2265 2270

Gly Ala Lys Pro Ser Val Lys Ser Glu Leu Ser Pro Val Ala Arg Gln
2275 2280 2285

Thr Ser Gln Ile Gly Gly Ser Ser Lys Ala Pro Ser Arg Ser Gly Ser
2290 2295 2300

Arg Asp Ser Thr Pro Ser Arg Pro Ala Gln Gln Pro Leu Ser Arg Pro
2305 2310 2315 2320

Ile Gln Ser Pro Gly Arg Asn Ser Ile Ser Pro Gly Arg Asn Gly Ile
2325 2330 2335

Ser Pro Pro Asn Lys Ile Ser Gln Leu Pro Arg Thr Ser Ser Pro Ser
2340 2345 2350

Thr Ala Ser Thr Lys Ser Ser Gly Ser Gly Lys Met Ser Tyr Thr Ser
2355 2360 2365

Pro Gly Arg Gln Met Ser Gln Gln Asn Leu Thr Lys Gln Thr Gly Leu
2370 2375 2380

Ser Lys Asn Ala Ser Ser Ile Pro Arg Ser Glu Ser Ala Ser Lys Gly
2385 2390 2395 2400

Leu Asn Gln Met Asn Asn Gly Asn Gly Ala Asn Lys Lys Val Glu Leu
2405 2410 2415

Ser Arg Met Ser Ser Thr Lys Ser Ser Gly Ser Glu Ser Asp Arg Ser
2420 2425 2430

Glu Arg Pro Val Leu Val Arg Gln Ser Thr Phe Ile Lys Glu Ala Pro
2435 2440 2445

Ser Pro Thr Leu Arg Arg Lys Leu Glu Glu Ser Ala Ser Phe Glu Ser
2450 2455 2460

Leu Ser Pro Ser Ser Arg Pro Ala Ser Pro Thr Arg Ser Gln Ala Gln
2465 2470 2475 2480

Thr Pro Val Leu Ser Pro Ser Leu Pro Asp Met Ser Leu Ser Thr His
2485 2490 2495

Ser Ser Val Gln Ala Gly Gly Trp Arg Lys Leu Pro Pro Asn Leu Ser
2500 2505 2510

Pro Thr Ile Glu Tyr Asn Asp Gly Arg Pro Ala Lys Arg His Asp Ile
2515 2520 2525

Ala Arg Ser His Ser Glu Ser Pro Ser Arg Leu Pro Ile Asn Arg Ser
2530 2535 2540

Gly Thr Trp Lys Arg Glu His Ser Lys His Ser Ser Ser Leu Pro Arg
2545 2550 2555 2560

Val Ser Thr Trp Arg Arg Thr Gly Ser Ser Ser Ser Ile Leu Ser Ala
2565 2570 2575

Ser Ser Glu Ser Ser Glu Lys Ala Lys Ser Glu Asp Glu Lys His Val
2580 2585 2590

Asn Ser Ile Ser Gly Thr Lys Gln Ser Lys Glu Asn Gln Val Ser Ala
2595 2600 2605

Lys Gly Thr Trp Arg Lys Ile Lys Glu Asn Glu Phe Ser Pro Thr Asn
2610 2615 2620

Ser Thr Ser Gln Thr Val Ser Ser Gly Ala Thr Asn Gly Ala Glu Ser
2625 2630 2635 2640

Lys Thr Leu Ile Tyr Gln Met Ala Pro Ala Val Ser Lys Thr Glu Asp
2645 2650 2655

Val Trp Val Arg Ile Glu Asp Cys Pro Ile Asn Asn Pro Arg Ser Gly
2660 2665 2670

Arg Ser Pro Thr Gly Asn Thr Pro Pro Val Ile Asp Ser Val Ser Glu
2675 2680 2685

Lys Ala Asn Pro Asn Ile Lys Asp Ser Lys Asp Asn Gln Ala Lys Gln
2690 2695 2700

Asn Val Gly Asn Gly Ser Val Pro Met Arg Thr Val Gly Leu Glu Asn
2705 2710 2715 2720

Arg Leu Asn Ser Phe Ile Gln Val Asp Ala Pro Asp Gln Lys Gly Thr
2725 2730 2735

Glu Ile Lys Pro Gly Gln Asn Asn Pro Val Pro Val Ser Glu Thr Asn
2740 2745 2750

Glu Ser Ser Ile Val Glu Arg Thr Pro Phe Ser Ser Ser Ser Ser Ser
2755 2760 2765

Lys His Ser Ser Pro Ser Gly Thr Val Ala Ala Arg Val Thr Pro Phe
2770 2775 2780

Asn Tyr Asn Pro Ser Pro Arg Lys Ser Ser Ala Asp Ser Thr Ser Ala
2785 2790 2795 2800

Arg Pro Ser Gln Ile Pro Thr Pro Val Asn Asn Asn Thr Lys Lys Arg
2805 2810 2815

Asp Ser Lys Thr Asp Ser Thr Glu Ser Ser Gly Thr Gln Ser Pro Lys
2820 2825 2830

Arg His Ser Gly Ser Tyr Leu Val Thr Ser Val
2835 2840

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CGGAATTCNN NNNNNNNAAC AGCNNNNNNN NNAATGAANN NCAAAGTCTG NNNTGAGGAT 60

CCTCA 65

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CGGAATTCGA CTCAGAANNN NNNAACTTCA GANNNNNNAT CNNNNNNNNN GTCTGAGGAT 60

CCTCA 65

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CGGAATTCNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNTGAGGAT 60

CCTCA 65

What is claimed is:

1. A composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids.

2. The composition of claim 1, wherein the cytoplasmic protein contains the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L), wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4.

3. The composition of claim 1, wherein the cytoplasmic protein contains the amino acid sequence SLGI.

4. The composition of claim 1, wherein the signal-transducing protein has at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

5. The composition of claim 1, wherein the composition comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic

compound, a polypeptide, or a protein.

6. The composition of claim 5, wherein the peptide comprises the sequence (S/T)-X-(V/I/L)-COOH, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

7. The composition of claim 6, wherein the peptide has the amino acid sequence DSENSNFRNEIQSLV.

8. The composition of claim 6, wherein the peptide has the amino acid sequence RNEIQSLV.

9. The composition of claim 6, wherein the peptide has the amino acid sequence NEIQSLV.

10. The composition of claim 6, wherein the peptide has the amino acid sequence EIQSLV.

11. The composition of claim 6, wherein the peptide has the amino acid sequence IQSLV.

12. The composition of claim 6, wherein the peptide has the amino acid sequence QSLV.

13. The composition of claim 6, wherein the peptide has the amino acid sequence SLV.

14. The composition of claim 6, wherein the peptide has the amino acid sequence IPPDSEDGNEEQSLV.

15. The composition of claim 6, wherein the peptide has

the amino acid sequence DSEMYNFRSQLASVV.

16. The composition of claim 6, wherein the peptide has the amino acid sequence IDLASEFLFLSNSFL.

17. The composition of claim 6, wherein the peptide has the amino acid sequence PPTCSQANSGRISTL.

18. The composition of claim 6, wherein the peptide has the amino acid sequence SDSNMNMNELSEV.

19. The composition of claim 6, wherein the peptide has the amino acid sequence QNFRTYIVSFV.

20. The composition of claim 6, wherein the peptide has the amino acid sequence RETIESTV.

21. The composition of claim 6, wherein the peptide has the amino acid sequence RGFISSLV.

22. The composition of claim 6, wherein the peptide has the amino acid sequence TIQSVI.

23. The composition of claim 6, wherein the peptide has the amino acid sequence ESLV.

24. The composition of claim 6, wherein the organic compound has the sequence Ac-SLV-COOH, wherein the Ac represents an acetyl, each - represent a peptide bond.

25. A composition capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such

parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein.

26. The composition of claim 25, wherein the composition comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

27. A method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, which comprises:

(a) contacting the cytoplasmic protein bound to the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the signal-transducing protein bound to the cytoplasmic protein and the bound cytoplasmic protein to form a complex; and
(b) detecting the displaced signal-transducing protein or the complex formed in step (a), wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein.

28. The method of claim 27, wherein the inhibition of specific binding between the signal-transducing

protein and the cytoplasmic protein affects the transcription activity of a reporter gene.

29. The method of claim 28, where in step (b) the displaced signal-transducing protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the signal-transducing protein is displaced.

30. The method of claim 27, wherein the cytoplasmic protein is bound to a solid support.

31. The method of claim 27, wherein the compound is bound to a solid support.

32. The method of claim 27, wherein the compound comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

33. The method of claim 27, wherein the contacting of step (a) is in vitro.

34. The method of claim 27, wherein the contacting of step (a) is in vivo.

35. The method of claim 34, wherein the contacting of step (a) is in a yeast cell.

36. The method of claim 34, wherein the contacting or step (a) is in a mammalian cell.

37. The method of claim 27, wherein the signal-

transducing protein is a cell surface receptor.

38. The method of claim 27, wherein the signal-transducing protein is a signal transducer protein.

39. The method of claim 27, wherein the signal-transducing protein is a tumor suppressor protein.

40. The method of claim 37, wherein the cell surface protein is the Fas receptor.

41. The method of claim 40, wherein the Fas receptor is expressed in cells derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

42. The method of claim 40, wherein the Fas receptor is expressed in cells comprising T-cells and B-cells.

43. The method of claim 37, wherein the cell-surface receptor is the CD4 receptor.

44. The method of claim 37, wherein the cell-surface receptor is the p75 receptor.

45. The method of claim 37, wherein the cell-surface receptor is the serotonin 2A receptor.

46. The method of claim 37, wherein the cell-surface receptor is the serotonin 2B receptor.

47. The method of claim 38, wherein the signal transducer protein is Protein Kinase-C-α-type.

48. The method of claim 39, wherein the tumor suppressor protein is adenomatosis polyposis coli tumor

suppressor protein.

49. The method of claim 39, wherein the tumor suppressor protein protein is the colorectal mutant cancer protein.

50. The method of claim 27, wherein the cytoplasmic protein contains the amino acid sequence SLGI, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids.

51. The method of claim 40, wherein the cytoplasmic protein is Fas-associated phosphatase-1.

52. A method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein, which comprises:

(a) contacting the signal-transducing protein bound to the cytoplasmic protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the cytoplasmic protein bound to the signal-transducing protein and the bound signal-transducing protein to form a complex; and

(b) detecting the displaced cytoplasmic protein or the complex of step (a) wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein.

53. The method of claim 52, wherein the inhibition of specific binding between the signal-transducing protein and the cytoplasmic protein affects the transcription activity of a reporter gene.

54. The method of claim 53, where in step (b) the displaced cytoplasmic protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the cytoplasmic protein is displaced.

55. The method of claim 52, wherein the cytoplasmic protein is bound to a solid support.

56. The method of claim 52, wherein the compound is bound to a solid support.

57. The method of claim 52, wherein the compound comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

58. The method of claim 52, wherein the contacting of step (a) is <u>in vitro</u>.

59. The method of claim 52, wherein the contacting of

step (a) is <u>in vivo</u>.

60. The method of claim 59, wherein the contacting of step (a) is in a yeast cell.

61. The method of claim 59, wherein the contacting or step (a) is in a mammalian cell.

62. The method of claim 52, wherein the signal-transducing protein is a cell surface receptor.

63. The method of claim 52, wherein the signal-transducing protein is a signal transducer protein.

64. The method of claim 52, wherein the signal-transducing protein is a tumor suppressor protein.

65. The method of claim 62, wherein the cell surface protein is the Fas receptor.

66. The method of claim 65, wherein the Fas receptor is expressed in cells derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

67. The method of claim 65, wherein the Fas receptor is expressed in cells comprising T-cells and B-cells.

68. The method of claim 62, wherein the cell-surface receptor is the CD4 receptor.

69. The method of claim 62, wherein the cell-surface receptor is the p75 receptor.

70. The method of claim 62, wherein the cell-surface receptor is the serotonin 2A receptor.

71. The method of claim 62, wherein the cell-surface receptor is the serotonin 2B receptor.

72. The method of claim 63, wherein the signal transducer protein is Protein Kinase-C-α-type.

73. The method of claim 64, wherein the tumor suppressor protein is adenomatosis polyposis coli tumor suppressor protein.

74. The method of claim 64, wherein the tumor suppressor protein is the colorectal mutant cancer protein.

75. The method of claim 52, wherein the cytoplasmic protein contains the amino acid sequence SLGI, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids.

76. The method of claim 52, wherein the cytoplasmic protein is Fas-associated phosphatase-1.

77. A method inhibiting the proliferation of cancer cells comprising the composition of claim 1.

78. The method of claim 77, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

79. The method of claim 77, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

80. A method of inhibiting the proliferation of cancer

cells comprising the composition of claim 25.

81. The method of claim 80, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

82. The method of claim 80, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

83. A method of inhibiting the proliferation of cancer cells comprising the compound identified by the method of claim 27.

84. The method of claim 83, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

85. The method of claim 83, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

86. A method of inhibiting the proliferation of cancer cells comprising the compound identified by the method of claim 52.

87. The method of claim 86, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

88. The method of claim 86, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

89. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the composition of claim 1

effective to result in apoptosis of the cells.

90. The method of claim 89, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

91. The method of claim 89, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

92. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the composition of claim 25 effective to result in apoptosis of the cells.

93. The method of claim 92, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

94. The method of claim 92, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

95. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the compound identified by the method of claim 27 effective to allow apoptosis of the cells.

96. The method of claim 95, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

97. The method of claim 95, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

98. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the compound identified by the method of claim 52 effective to result in apoptosis of the cells.

99. The method of claim 98, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

100. The method of claim 98, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

101. A method of inhibiting the proliferation of virally infected cells comprising the composition of claim 1.

102. A method of inhibiting the proliferation of virally infected cells comprising the composition of claim 25.

103. A method of inhibiting the proliferation of virally infected cells comprising the compound identified by the method of claim 27.

104. A method of inhibiting the proliferation of virally infected cells comprising the compound identified by the method of claim 52.

105. The method of claim 101, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

106. The method of claim 102, wherein the virally

infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

107. The method of claim 103, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

108. The method of claim 104, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

109. A method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells the composition of claim 1 effective to result in apoptosis of the cells.

110. A method of treating a virally-infected subject which comprises introducing to the subject's virally infected cells the composition of claim 25 effective to result in apoptosis of the cells.

111. A method of treating a virally-infected subject which comprises introducing to the subject's virally-infected cells an amount of the compound identified by the method of claim 27 effective to result in apoptosis of the cells.

112. A method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells an amount of the compound identified by the method of claim 52 effective to

result in apoptosis of the cells.

113. The method of claim 109, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

114. The method of claim 110, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

115. The method of claim 111, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

116. The method of claim 112, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphtropic virus, type 1 or HIV.

117. A pharmaceutical composition comprising the composition of claim 1 in an effective amount and a pharmaceutically acceptable carrier.

118. A pharmaceutical composition comprising the composition of claim 25 in an effective amount and a pharmaceutically acceptable carrier.

119. A pharmaceutical composition comprising the compound identified by the method of claim 27 in an effective amount and a pharmaceutically acceptable carrier.

120. A pharmaceutical composition comprising the compound identified by the method of claim 52 in an effective amount and a pharmaceutically acceptable carrier.

FIG. 1

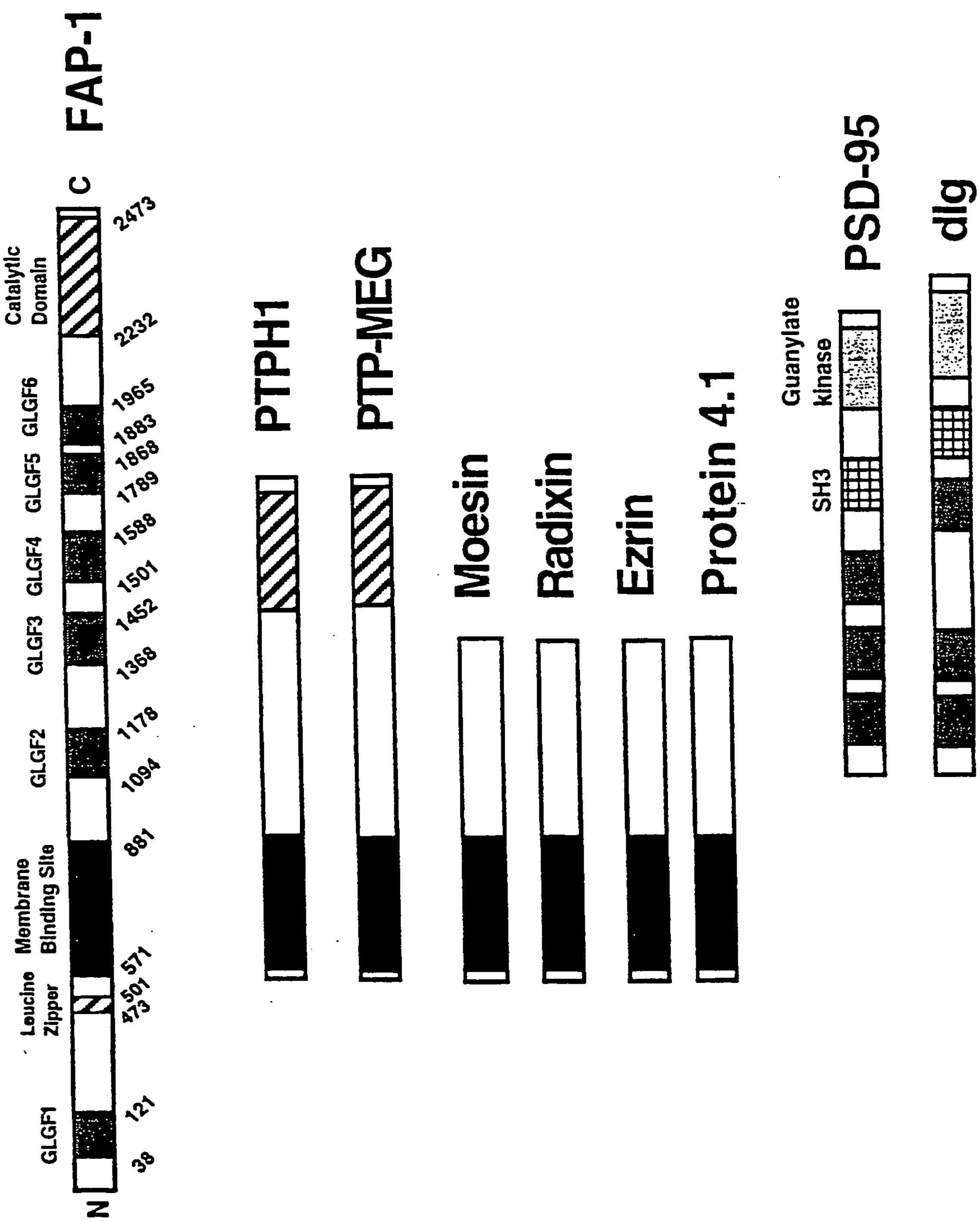
FAP-1
N
C
GLGF1
Leucine Zipper
Membrane Binding Site
GLGF2
GLGF3
GLGF4
GLGF5
GLGF6
Catalytic Domain
38
121
473
501
571
881
1094
1178
1368
1452
1501
1588
1789
1868
1883
1965
2232
2473
PTPH1
PTP-MEG
Moesin
Radixin
Ezrin
Protein 4.1
SH3
Guanylate kinase
PSD-95
dlg

FIG. 2A

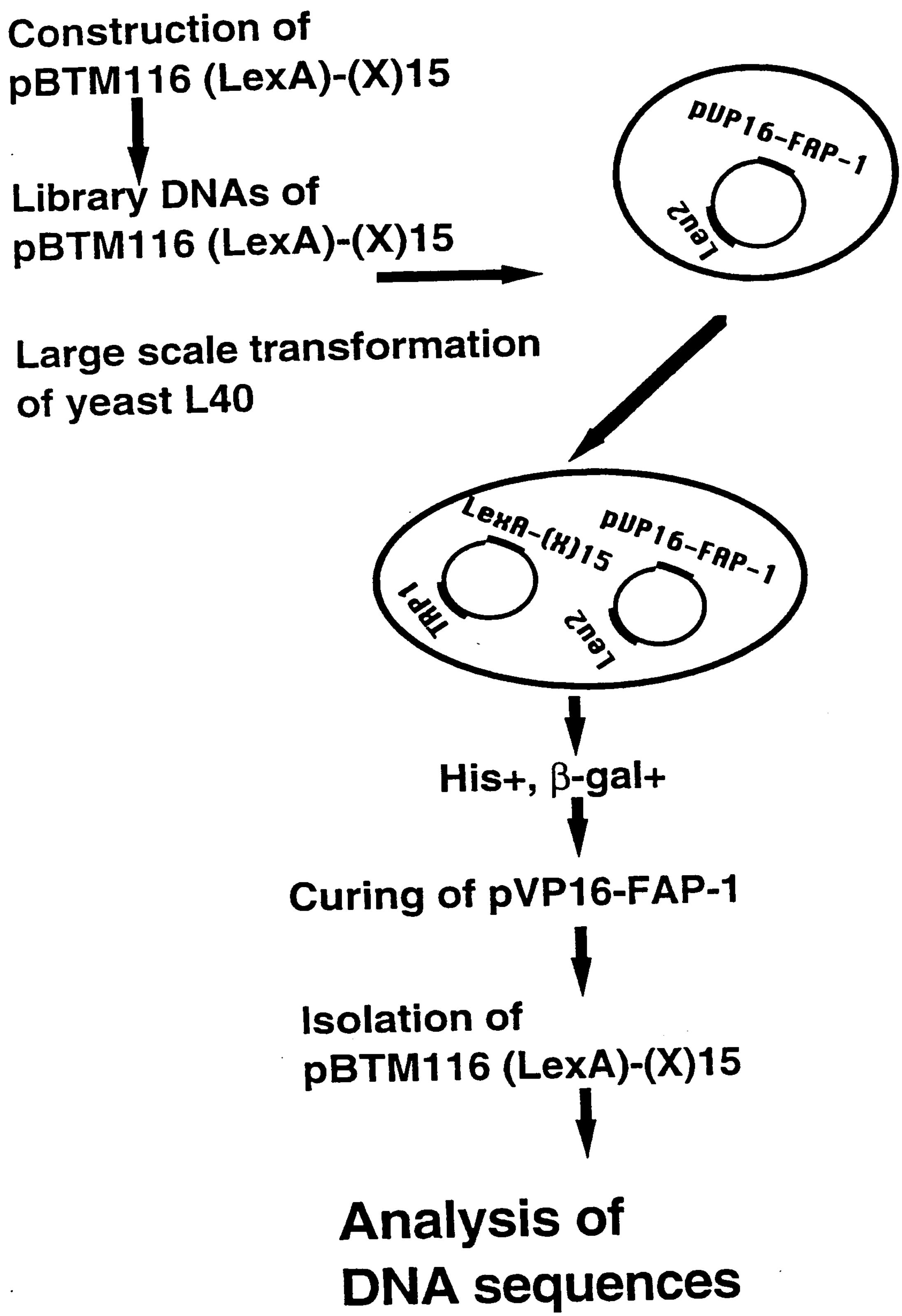
Construction of
pBTM116 (LexA)-(X)15
Library DNAs of
pBTM116 (LexA)-(X)15
pVP16-FAP-1
Leu2
Large scale transformation
of yeast L40
LexA-(X)15
TRP1
pVP16-FAP-1
Leu2
His+, β-gal+
Curing of pVP16-FAP-1
Isolation of
pBTM116 (LexA)-(X)15
Analysis of
DNA sequences

FIG. 2B

Human	D	S	E	N	S	N	F	R	N	E	I	Q	S	L	V
Rat	S	I	S	N	S	R	N	E	N	E	G	Q	S	L	E
Mouse	S	T	P	D	T	G	N	E	N	E	G	Q	C	L	E

FIG. 2C

-	-	-	N	S	-	-	-	N	E	-	Q	S	L	-	
C	Y	A			A	I	G			L				V	12-0
E	N	A			G	V	S			E				V	5-0
W	W	G			A	T	Q			P				V	13-0
E	H	A			Q		Q			Q				V	20-0
N	S	S			F	H	S			L				V	6-2
G	L	R			L	P	P			D				V	9-5
G	S	D			S	G	V			N				V	18-1
D	K	K			R	P	V			N				V	22-1
T	G	K			D	V	W			A				V	71-1
A	S	R			N	E	E			L				I	14-5

FIG. 2D

I	P	P	D	S	E	D	G	N	E	E	Q	S	L	V	8-1
D	S	E	M	Y	N	F	R	S	Q	L	A	S	V	V	9-3
I	D	L	A	S	E	F	L	F	L	S	N	S	F	L	14-1
P	P	T	C	S	Q	A	N	S	G	R	I	S	T	L	0-2
		S	D	S	N	M	N	M	N	E	L	S	E	V	57-5
				Q	N	F	R	T	Y	I	V	S	F	V	72-1
							R	E	T	I	E	S	T	V	25-9
							R	G	F	I	S	S	L	V	16-13
									T	I	Q	S	V	I	6-3
											E	S	L	V	18-1

Consensus: *t* S-X-V/L/I

FIG. 3A

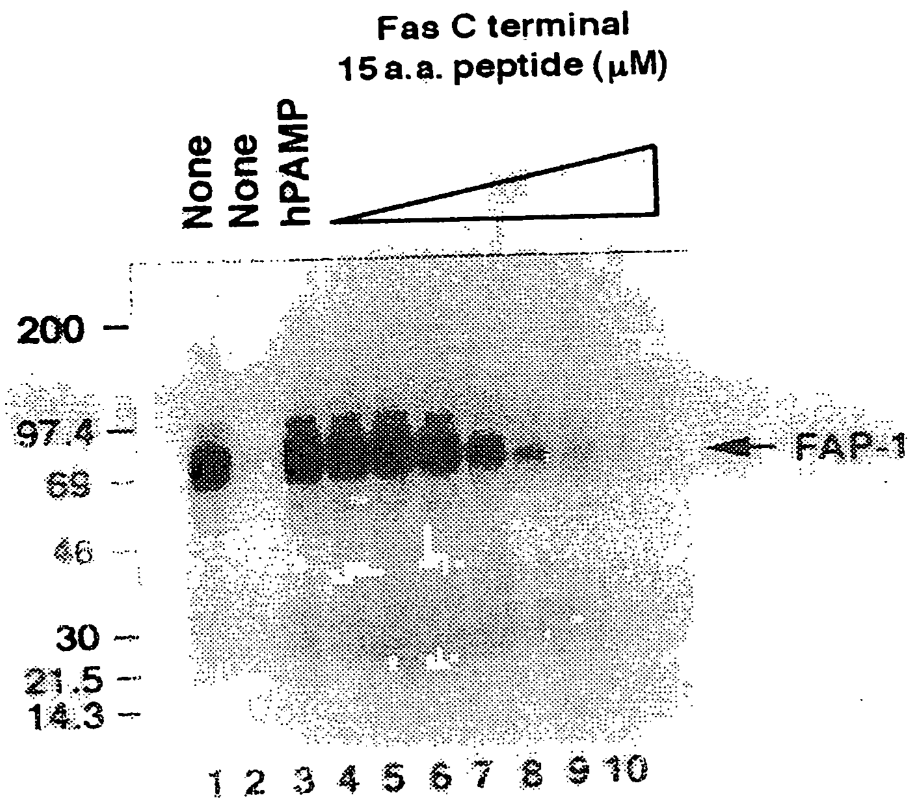
Fas C terminal
15 a.a. peptide (μM)
None
None
hPAMP
200
97.4
69
46
30
21.5
14.3
FAP-1
1 2 3 4 5 6 7 8 9 10

FIG. 3B

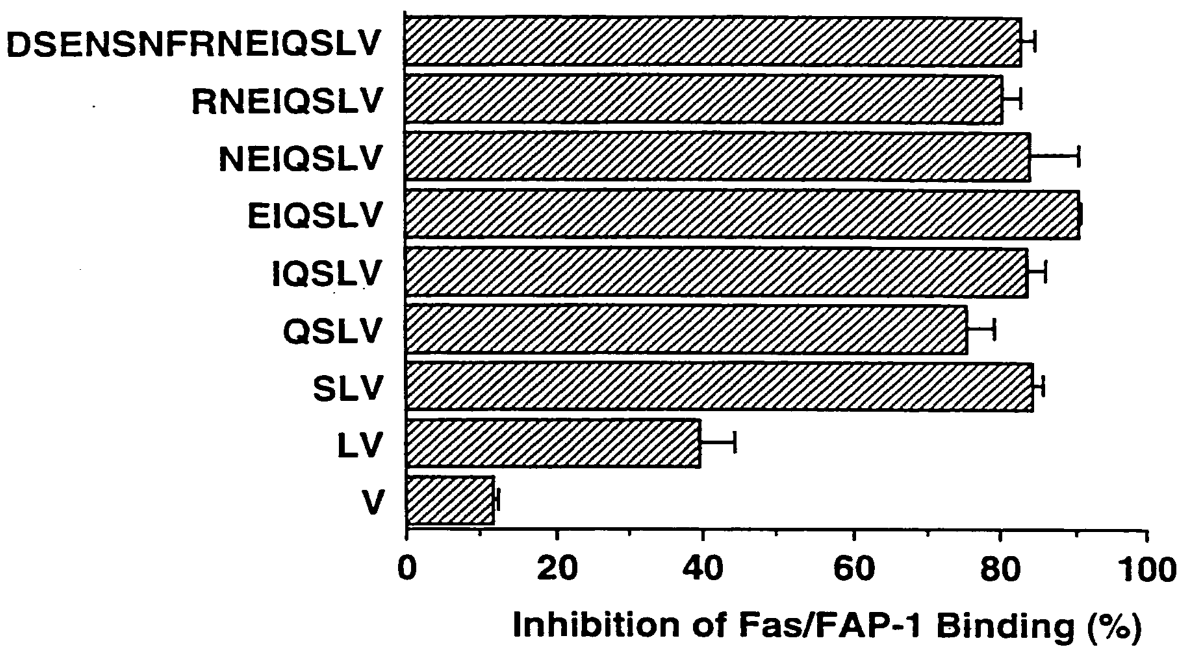
DSENSNFRNEIQSLV
RNEIQSLV
NEIQSLV
EIQSLV
IQSLV
QSLV
SLV
LV
V
0
20
40
60
80
100
Inhibition of Fas/FAP-1 Binding (%)

FIG. 3C

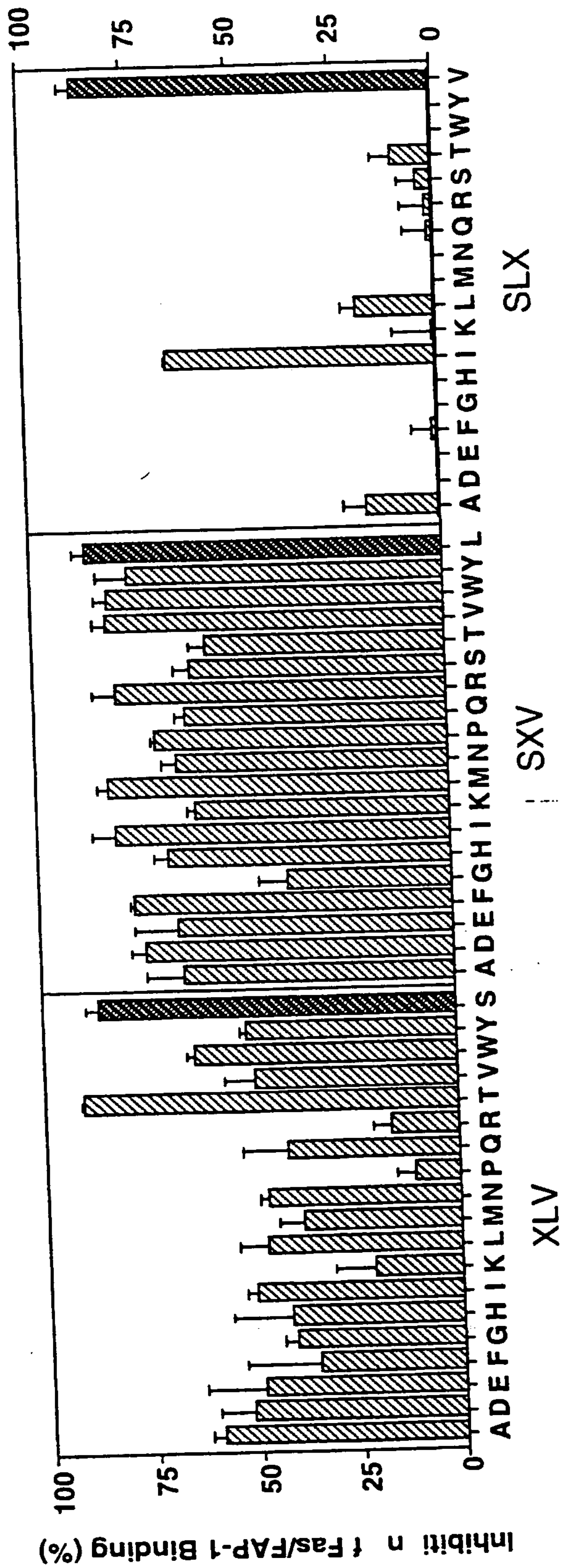
Inhibiti n f Fas/FAP-1 Binding (%)
100
75
50
25
0
A D E F G H I K L M N P Q R T V W Y S
A D E F G H I K M N P Q R S T V W Y L
A D E F G H I K L M N Q R S T W Y V
XLV
SXV
SLX

FIG. 4A

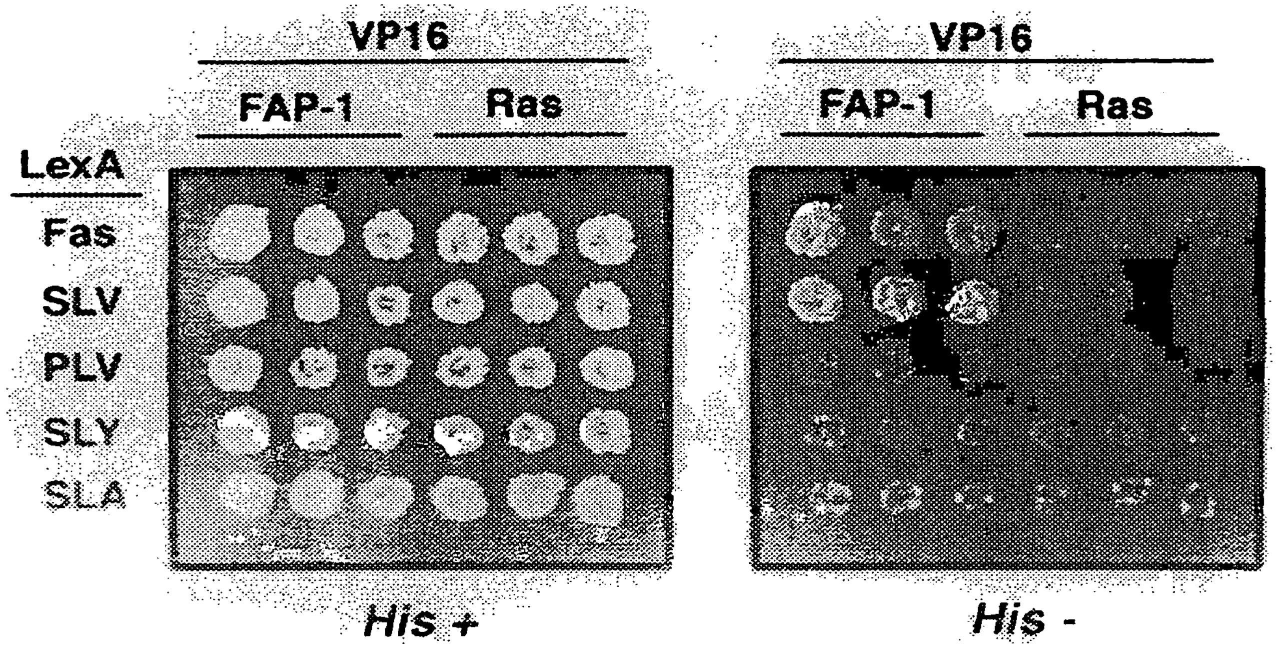

FIG. 4B

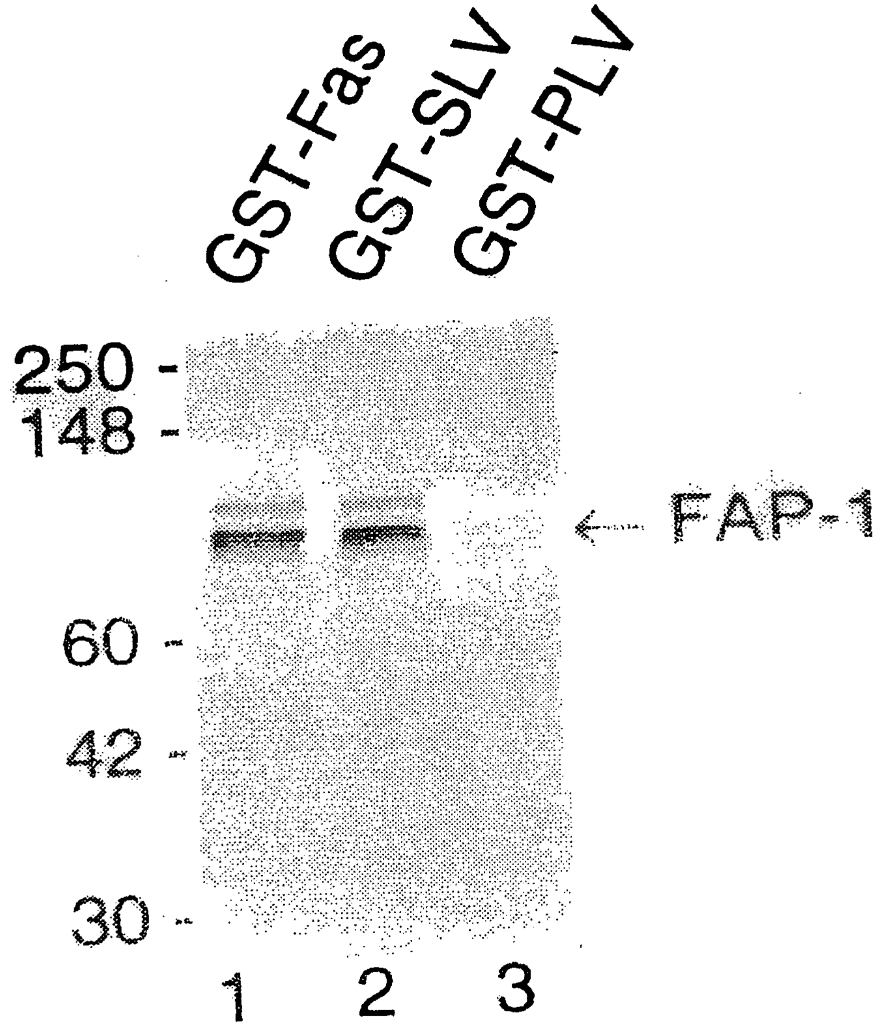

FIG. 4C

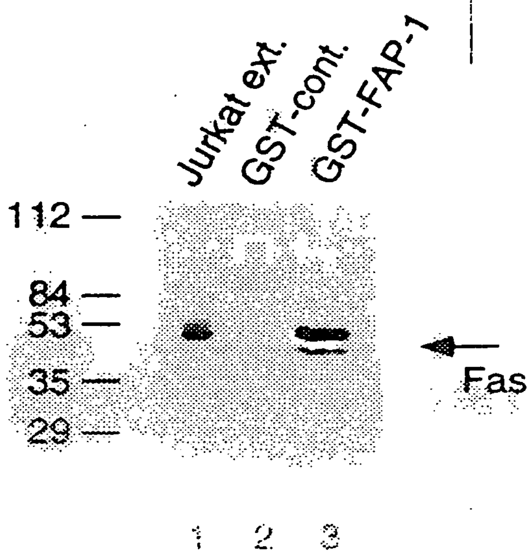
Jurkat ext.
GST-cont.
GST-FAP-1
112
84
53
35
29
Fas
1 2 3

FIG. 4D

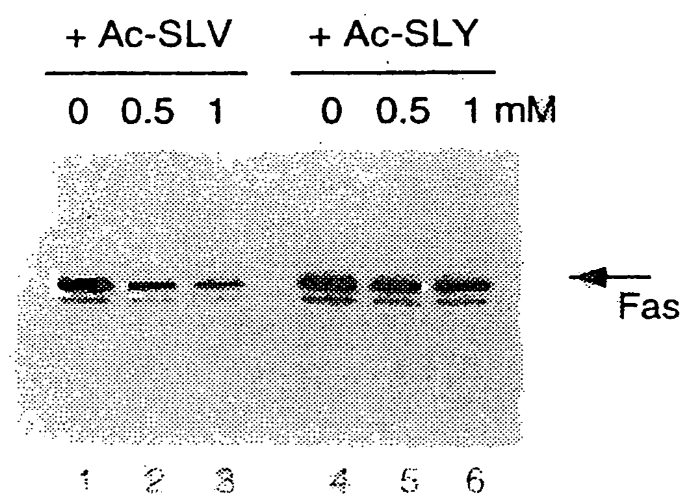
+ Ac-SLV
+ Ac-SLY
0 0.5 1 0 0.5 1 mM
Fas
1 2 3 4 5 6

FIG. 5B
Ac-SLY-OH

FIG. 5A
Ac-SLY-OH

FIG. 5D
Ac-SLY-OH

FIG. 5C
Ac-SLV-OH

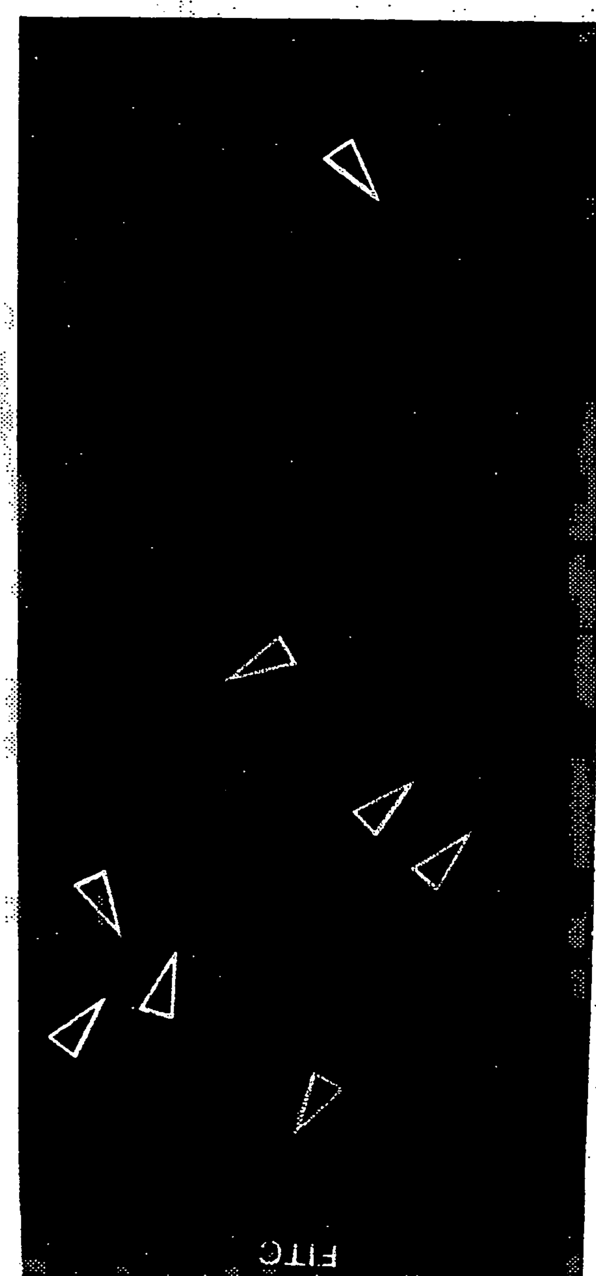

FIG. 5F
Ac-SLY-OH

FIG. 5E
Ac-SLV-OH

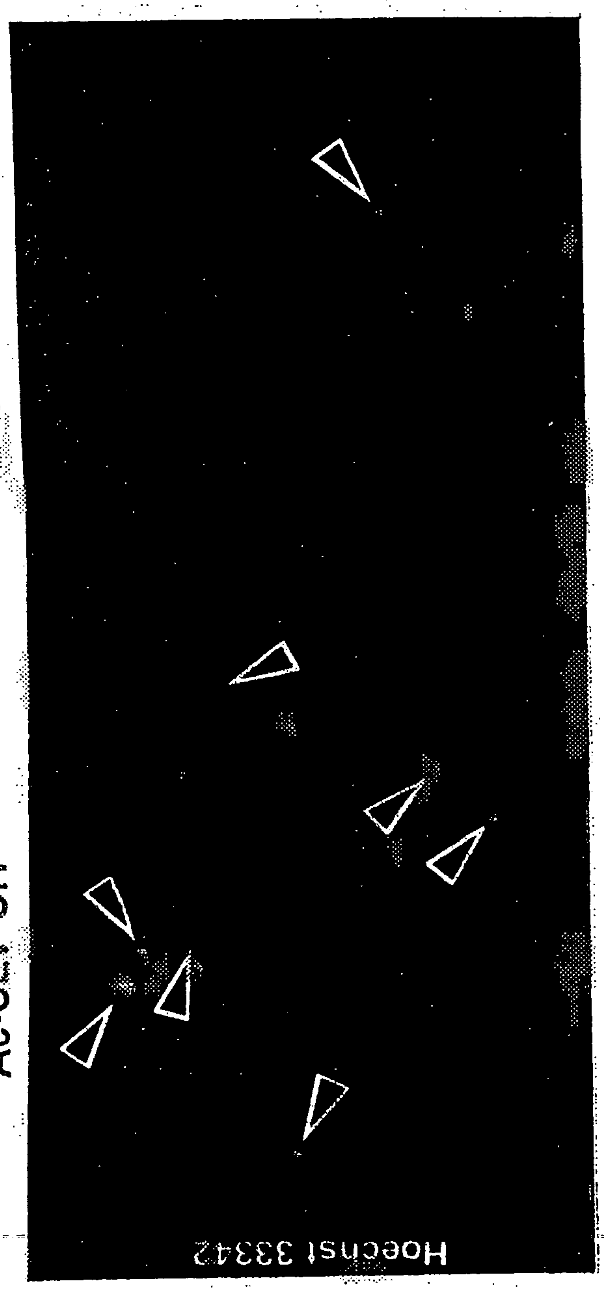

FIG. 6

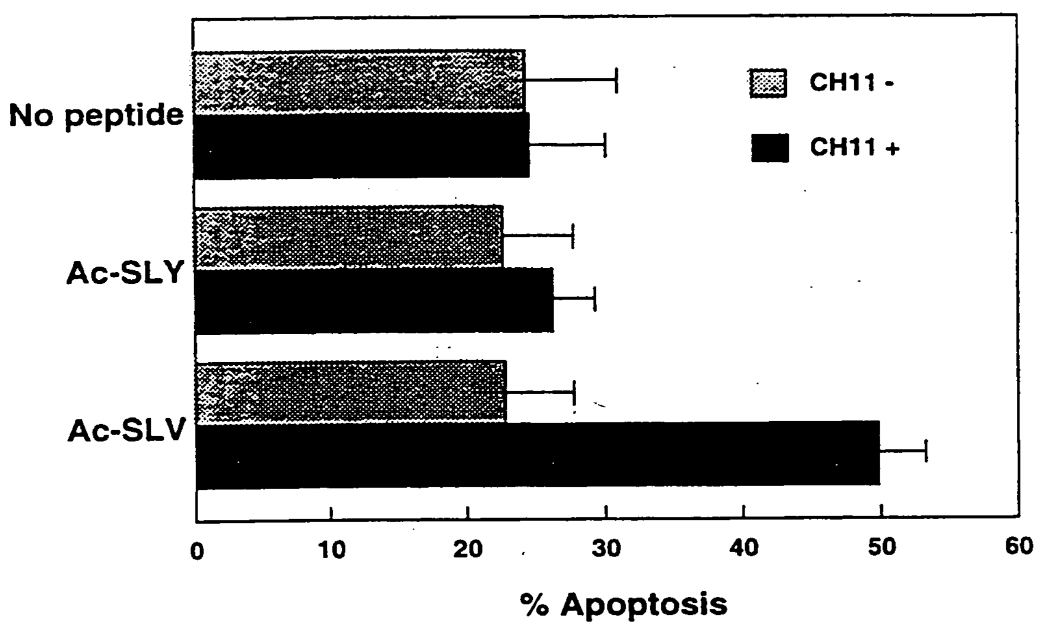

FIG. 7A

NGF Receptor

```
  1 mgagatgram dgprllllll lgvslggake acptglyths gecckacnlg egvaqpcgan
 61 qtvcepclds vtfsdvvsat epckpctecv glqsmsapcv eaddavcrca ygyyqdettg
121 rceacrvcea gsglvfscqd kqntvceecp dgtysdeanh vdpclpctvc edterqlrec
181 trwadaecee ipgrwitrst ppegsdstap stqepeappe qdliastvag vvttvmgssq
241 pvvtrgttdn lipvycsila avvvglvayi afkrwnsckq nkqgansrpv nqtpppegek
301 lhsdsgisvd sqslhdqqph tqtasgqalk gdgglysslp pakreevekl lngsagdtwr
361 hlagelgyqp ehidsfthea cpvrallasw atqdsatlda llaalrriqr adlveslcse
421 statspv
```

FIG. 7B

CD4 Receptor

```
  1 mnrgvpfrhl llvlqlallp aatqgkkvvl gkkgdtvelt ctasqkksiq fhwknsnqik
 61 ilgnqgsflt kgpsklndra dsrrslwdqg nfpliiknlk iedsdtyice vedqkeevql
121 lvfgltansd thllqgqslt ltlesppgss psvqcrsprg kniqggktls vsqlelqdsg
181 twtctvlqnq kkvefkidiv vlafqkassi vykkegeqve fsfplaftve kltgsgelww
241 qaerassks witfdlknke vsvkrvtqdp klqmgkklpl hltlpqalpq yagsgnltla
301 leaktgklhq evnlvvmrat qlqknltcev wgptspklml slklenkeak vskrekavwv
361 lnpeagmwqc llsdsgqvll esnikvlptw stpvqpmali vlggvaglll figlgiffcv
421 rcrhrrrqae rmsqikrlls ekktcqcphr fqktcspi
```

FIG. 7C

Species	C-terminal sequences of NGFR (p75)	Binding activity of FAP-1
Human	fSESTATSPV-COOH	+
Rat	fSESTATSPV-COOH	+
Chicken	fSESTATSPV-COOH	+

FIG. 7D

```
  1 mnsgvamkyg ndssaelsel hsaalaslkg divelnkrlq qtererdlle kklakaqceq
 61 shlmrehedv qerttlryee ritelhsvia elnkkidrlq gttireedey selrselsqs
121 qhevnedsrs mdqdqtsvsi penqstmvta dmdncsdlns elqrvltgle nvvcgrkkss
181 cslsvaevdr hieqlttase hcdlaiktve eiegvlgrdl ypnlaeersr wekelaglre
241 enesltamlc skeeelnrtk atmnaireer drlrrrvrel qtrlqsvqat gpsspgrlts
301 tnrpinpstg elstssssnd ipiakiaerv klsktrsess ssdrpvlgse issigvsssv
361 aehlahslqd csniqeifqt lyshgsaise skirefevet erlnsriehl ksqndlltit
421 leecksnaer msmlvgkyes natalrlalq yseqcieaye lllalaeseq slilgqfraa
481 gvgsspgdqs gdenitqmlk rahdcrktae naakallmkl dgscggafav agcsvqpwes
541 lssnshtstt sstasscdte ftkedeqrlk dyiqqlkndr aavkltmlel esihidplsy
601 dvkprgdsqr ldlenavlmq elmamkeema elkaqlylle kekkalelkl streaqeqay
661 lvhiehlkse veeqkeqrmr slsstssgsk dkpgkecada aspalslael rttcsenela
721 aeftnairre kklkarvqel vsalerltks seirhqqsae fvndlkrans nlvaayekak
781 kkhqnklkkl esqmmamver hetqvrmlkq rialleeens rphtnetsl
```

FIG. 7E

```
  1 madvfpgnds tasqdvanrf arkgalrqkn vhevkdhkfi arffkqptfc shctdfiwgf
 61 gkqgfqcqvc cfvvhkrche fvtfscpgad kgpdtddprs khkfkihtyg sptfcdhcgs
121 llyglihqgm kcdtcdmnvh kqcvinvpsl cgmdhtekrg riylkaevad eklhvtvrda
181 knlipmdpng lsdpyvklkl ipdpkneskq ktktirstln pqwnesftfk lkpsdkdrrl
241 sveiwdwdrt trndfmgsls fgvselmkmp asgwykllnq eegeyynvpi pegdeegnme
301 lrqkfekakl gpagnkvisp sedrkqpsnn ldrvkltdfn flmvlgkgsf gkvmladrkg
361 teelyaikil kkdvviqddd vectmvekrv lalldkppfl tqlhscfqtv drlyfvmeyv
421 nggdlmyhiq qvgkfkepqa vfyaaeisig lfflhkrgii yrdlkldnvm ldseghikia
481 dfgmckehmm dgvttrtfcg tpdyiapeii ayqpygksvd wwaygvllye mlagqppfdg
541 ededelfqsi mehnvsypks lskeavsick glmtkhpakr lgcgpegerd vrehaffrri
601 dweklenrei qppfkpkvcg kgaenfdkff trgqpvltpp dqlvianidq sdfegfsyvn
661 pqfvhpilqs av
```

FIG. 7F

```
  1 mdilceents lssttnslmq lnddtrlysn dfnsgeants dafnwtvdse nrtnlscegc
 61 lspsclsllh lqeknwsall tavviiltia gnilvimavs lekklqnatn yflmslaiad
121 mllgflvmpv smltilygyr wplpsklcav wiyldvlfst asimhlcais ldryvaiqnp
181 ihhsrfnsrt kaflkiiavw tisvgismpi pvfglqddsk vfkegsclla ddnfvligsf
241 vsffipltim vityfltiks lqkeatlcvs dlgtraklas fsflpqssls seklfqrsih
301 repgsytgrr tmqsisneqk ackvlgivff lfvvmwcpff itnimavick escnedviga
361 llnvfvwigy lssavnplvy tlfnktyrsa fsryiqcqyk enkkplqlil vntipalayk
421 ssqlqmgqkk nskqdakttd ndcsmvalgk qhseeaskdn sdgvnekvsc v
```

FIG. 7G

```
  1 malsyrvsel qstipehilq stfvhvissn wsglqtesip eemkqiveeq gnklhwaall
 61 ilmviiptig gntlvilavs lekklqyatn yflmslavad llvglfvmpi alltimfeam
121 wplplvlcpa wlfldvlfst asimhlcais vdryiaikkp iqanqynsra tafikitvvw
181 lisigiaipv pikgietdvd npnnitcvlt kerfgdfmlf gslaafftpl aimivtyflt
241 ihalqkkayl vknkppqrlt wltvstvfqr detpcsspek vamldgsrkd kalpnsgdet
301 lmrrtstigk ksvqtisneq raskvlgivf flfllmwcpf fitnitlvlc dscnqttlqm
361 lleifvwigy vssgvnplvy tlfnktfrda fgryitcnyr atksvktlrk rsskiyfrnp
421 maenskffkk hgirnginpa myqspmrlrs stiqsssiil ldtllltene gdkteeqvsy
481 v
```

FIG. 7H

1 maaasydqll kqvealkmen snlrqeledn snhltklete asnmkevlkq lqgsiedeam
61 assgqidlle rlkelnldss nfpgvklrsk mslrsygsre gsvssrsgec spvpmgsfpr
121 rgfvngsres tgyleeleke rsllladldk eekekdwyya qlqnltkrid slpltenfsl
181 qtdmtrrqle yearqirvam eeqlgtcqdm ekraqrriar iqqiekdilr irqllqsqat
241 eaerssqnkh etgshdaerq negqgvgein matsgngqgs ttrmdhetas vlssssthsa
301 prrltshlgt kvemvyslls mlgthdkddm srtllamsss qdscismrqs gclplliqll
361 hgndkdsvll gnsrgskear arasaalhni ihsqpddkrg rreirvlhll eqiraycetc
421 wewqeahepg mdqdknpmpa pvehqicpav cvlmklsfde ehrhamnelg glqaiaellq
481 vdcemygltn dhysitlrry agmaltnltf gdvankatlc smkgcmralv aqlksesedl
541 qqviasvlrn lswradvnsk ktlrevgsvk almecalevk kestlksvls alwnlsahct
601 enkadicavd galaflvgtl tyrsqtntla iiesgggilr nvssliatne dhrqilrenn
661 clqtllqhlk shsltivsna cgtlwnlsar npkdqealwd mgavsmlknl ihskhkmiam
721 gsaaalrnlm anrpakykda nimspgsslp slhvrkqkal eaeldaqhls etfdnidnls
781 pkashrskqr hkqslygdyv fdtnrhddnr sdnfntgnmt vlspylnttv lpssssrgs
841 ldssrsekdr slerergigl gnyhpatenp gtsskrglqi sttaaqiakv meevsaihts
901 qedrssgstt elhcvtdern alrrssaaht hsntynftks ensnrtcsmp yakleykrss
961 ndslnsvsss dgygkrgqmk psiesysedd eskfcsygqy padlahkihs anhmddndge
1021 ldtpinyslk ysdeqlnsgr qspsqnerwa rpkhiiedei kqseqrqsrn qsttypvyte
1081 stddkhlkfq phfgqqecvs pyrsrgangs etnrvgsnhg inqnvsqslc qeddyeddkp
1141 tnyserysee eqheeeerpt nysikyneek rhvdqpidys lkyatdipss qkqsfsfsks
1201 ssgqsskteh mssssentst pssnakrqnq lhpssaqsrs gqpqkaatck vssinqetiq
1261 tycvedtpic fsrcsslssl ssaedeigcn qttqeadsan tlqiaeikek igtrsaedpv
1321 sevpavsqhp rtkssrlqgs slssesarhk avefssgaks psksgaqtpk sppehyvqet
1381 plmfsrctsv ssldsfesrs iassvqsepc sgmvsgiisp sdlpdspgqt mppsrsktpp
1441 pppqtaqtkr evpknkapta ekresgpkqa avnaavqrvq vlpdadtllh fatestpdgf
1501 scssslsals ldepfiqkdv elrimppvqe ndngnetese qpkesnenqe keaektidse
1561 kdllddsddd dieileecii sampTkssrk akkpaqtask lpppvarkps qlpvykllps
1621 qnrlqpqkhv sftpgddmpr vycvegtpin fstatslsdl tiesppnela agegvrggaq
1681 sgefekrdti ptegrstdea qggktssvti pelddnkaee gdilaecins ampkgkshkp
1741 frvkkimdqv qqasasssap nknqldgkkk kptspvkpip qnteyrtrvr knadsknnln
1801 aervfsdnkd skkqnlknns kdfndklpnn edrvrgsfaf dsphhytpie gtpycfsrnd
1861 slssldfddd dvdlsrekae lrkakenkes eakvtshtel tsnqqsankt qaiakqpinr
1921 gqpkpilqkq stfpqsskdi pdrgaatdek lqnfaientp vcfshnssls slsdidqenn
1981 nkenepiket eppdsqgeps kpqasgyapk sfhvedtpvc fsrnsslssl sidseddllq
2041 ecissampkk kkpsrlkgdn ekhsprnmgg ilgedltldl kdiqrpdseh glspdsenfd
2101 wkaiqegans ivsslhqaaa aaclsrqass dsdsilslks gislgspfhl tpdqeekpft
2161 snkgprilkp gekstletkk ieseskgikg gkkvykslit gkvrsnseis gqmkqplqan
2221 mpsisrgrtm ihipgvrnss sstspvskkg pplktpasks psegqtatts prgakpsvks
2281 elspvarqts qiggsskaps rsgsrdstps rpaqqplsrp iqspgrnsis pgrngisppn
2341 klsqlprtss pstastkssg sgkmsytspg rqmsqqnltk qtglsknass iprsesaskg
2401 lnqmnngnga nkkvelsrms stkssgsesd rserpvlvrq stfikeapsp tlrrkleesa
2461 sfeslspssr pasptrsqaq tpvlspslpd mslsthssvq aggwrklppn lsptieyndg
2521 rpakrhdiar shsespsrlp inrsgtwkre hskhssslpr vstwrrtgss ssilsasses
2581 sekaksedek hvnsisgtkq skenqvsakg twrkikenef sptnstsqtv ssgatngaes
2641 ktliyqmapa vsktedvwvr iedcpinnpr sgrsptgntp pvidsvseka npnikdskdn
2701 qakqnvgngs vpmrtvglen rlnsfiqvda pdqkgteikp gqnnpvpvse tnessivert
2761 pfssssssskh sspsgtvaar vtpfnynpsp rkssadstsa rpsqiptpvn nntkkrdskt
2821 dstessgtqs pkrhsgsylv <u>tsv</u>

FIG. 8

p75NGFR
(Low-affinity nerve growth factor receptor)

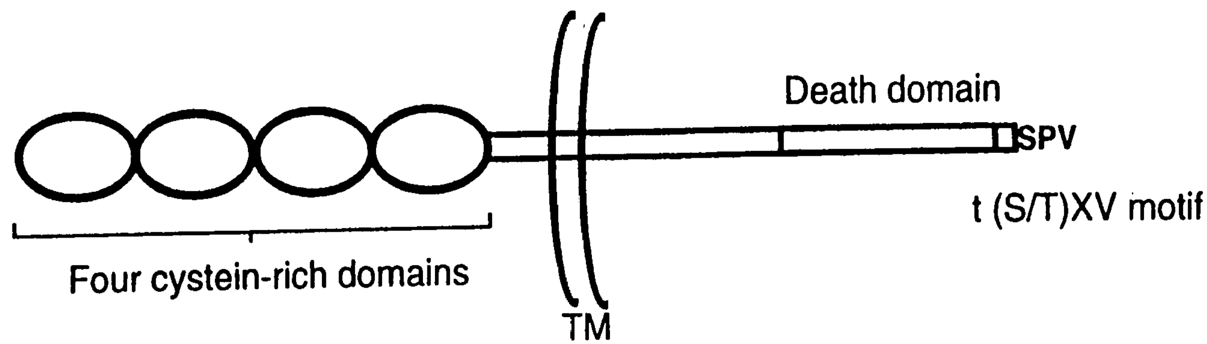

FIG. 9

	C-terminal amino acid sequence
Fas	NEIQ$\boxed{\text{SLV}}$
p75NGFR	STAT$\boxed{\text{SPV}}$

$\boxed{\textbf{t (S/T)-X-V}}$ – COOH $\longleftrightarrow$ **PDZ domain**

interaction

FIG. 10

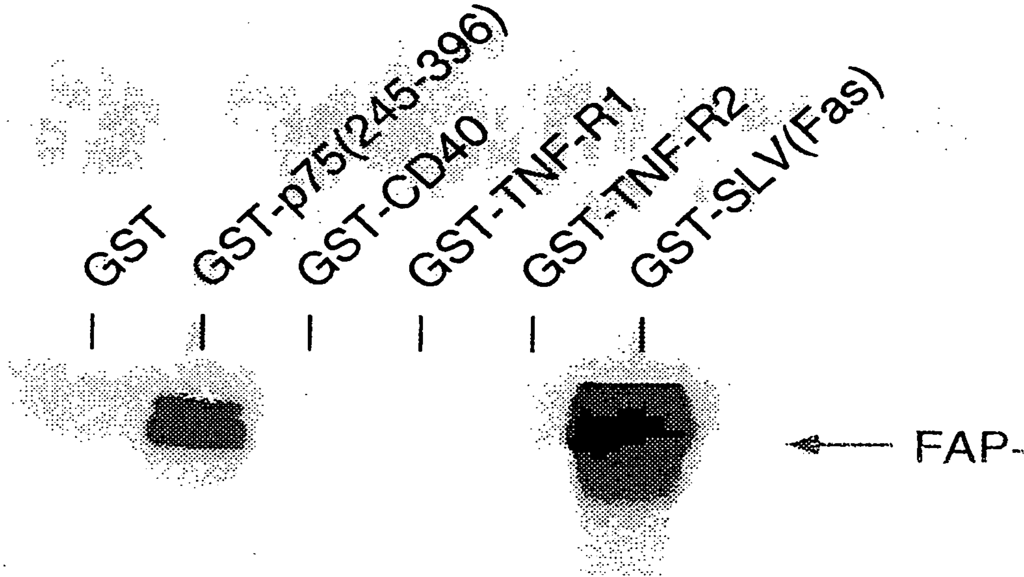
GST
GST-p75(245-396)
GST-CD40
GST-TNF-R1
GST-TNF-R2
GST-SLV(Fas)
FAP-

FIG. 11A

FAP-1 binds to C-terminal three amino acids SPV of p75NGFR.

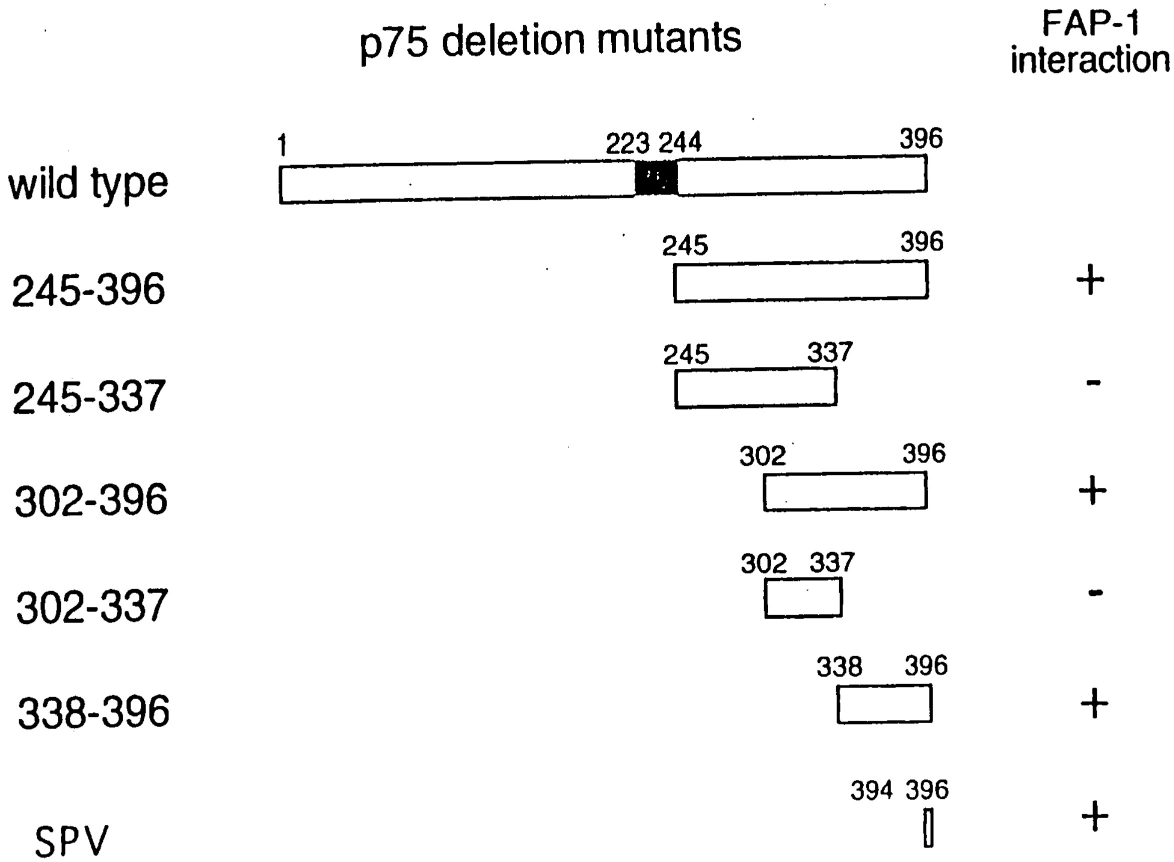

FIG. 11B

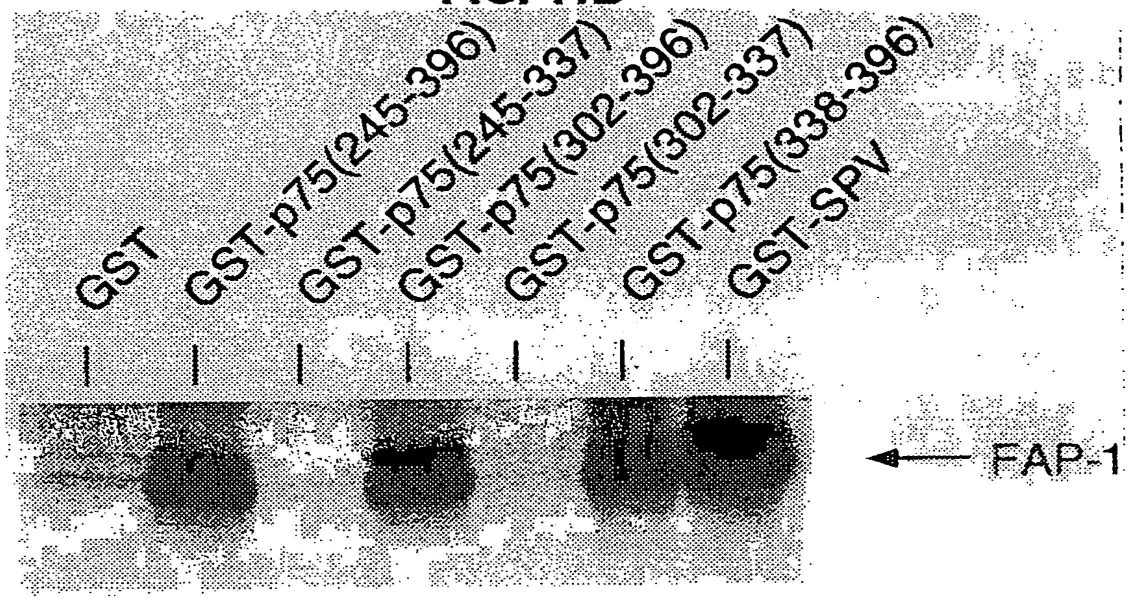
GST
GST-p75(245-396)
GST-p75(245-337)
GST-p75(302-396)
GST-p75(302-337)
GST-p75(338-396)
GST-SPV
FAP-1

FIG. 12

FAP-1 binds to p75NGFR C-terminal cytoplasmic region in yeast.

	VP16-FAP-1	VP16-cRaf
LexA-p75NGFR(338-396)	+	-
LexA-p75NGFR(365-396)	+	-
LexA-Fas	++	-
LexA-Ras^{V12}	-	+
LexA-Lamin	-	-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12677

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :424/198.1; 514/2; 530/351; 435/7.1, 7.23
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/198.1; 514/2; 530/351; 435/7.1, 7.23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DOYLE. D.A. et al. "Crystal Structures of a Complexed and Peptide-Free Membrane Protein-Binding Domain: Molecular Basis of Peptide Recognition by PDZ." Cell. June 1996. Vol. 85. pages 1067-1076, especially page 1067.	1-120
Y	MATSUMINE. A. et al. "Binding of APC to the Human Homolog of the Drosophila Discs Large Tumor Suppressor Protein." Science. May 1996. Vol. 272. No. 5264. pages 1020-1023, especially page 1020.	1-120
Y	KORNAU. H.-C. et al. "Domain Interaction Between NMDA Receptor Subunits and the Postsynaptic Density Protein PSD-95." Science. September 1995. Vol. 269. No. 5231. pages 1737-1740, especially page 1737.	1-120

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search 09 OCTOBER 1997	Date of mailing of the international search report 09 JAN 1998
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INTERNATIONAL SEARCH REPORT

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,632,994 A (REED et al) 27 May 1997, col. 2, lines 12-56.	1-120
Y	WO 96/18641 A1 (YEDA RESEARCH AND DEVELOPMENT CO. LTD.) 20 June 1996. pages 1-57, especially page 6	1-120
Y	ZHANG. J. et al. "A Mouse Fas-Associated Protein with Homology to the Human MORT1/FADD Protein is Essential for Fas-Induced Apoptosis." Molecular and Cellular Biology. June 1996. Vol. 16. No. 6. pages 2756-2763, especially page 2756.	1-120

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12677

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 38/00, 39/00; C07K 1/00, 14/00, 17/00; G01N 33/53, 33/567, 33/574

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